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CONTENTS OF VOLUME VIII

JULY, 1911. NUMBER 1

PAGE

MENINGOCOCCUS ENDOCARDITIS, WITH SEPTICEMIA. ITS BEARING ON THE MODE OF INFECTION IN EPIDEMIC CEREBROSPINAL MENINGITIS. RUSSELL L. CECIL, M.D., AND WILLARD B. SOPER, M.D., NEW YORK 1

A PHYSIOLOGICAL INVESTIGATION OF THE TREATMENT IN HEMOPTYSIS. CARL J. WIGGERS, M.D., ANN ARBOR, MICH 17

POSTANESTHETIC GLYCOSURIA. P. B. HAWK, URBANA, ILL 39

POSTANESTHETIC GLYCOSURIA OF SURGICAL PATIENTS. JOHN M. SWAN, M.D., WATKINS, N. Y. 58

MALIGNANT TUMORS OF THE ADRENAL. BENJAMIN F. DAVIS, CHICAGO 60

HEMOCHROMATOSIS. A REPORT OF THREE CASES AND A DISCUSSION OF THE PATHOGENESIS. T. P. SPRUNT, M.D., BALTIMORE 75

BOOK REVIEWS:—DYSPEPSIA: ITS VARIETIES AND TREATMENT. BY W. SOLTAU FENWICK, M.D. 130

DIAGNOSTIC AND THERAPEUTIC TECHNIC. BY ALBERT S. MORROW, M.D. 131

AUGUST, 1911. NUMBER 2

CEREBROSPINAL MENINGITIS DUE TO BACILLUS INFLUENZÆ. A REPORT OF TWO CASES, FROM ONE OF WHICH THE ORGANISM WAS OBTAINED IN PURE CULTURE FROM THE CIRCULATING BLOOD EIGHTY-FIVE DAYS BEFORE DEATH. LAWRENCE J. RHEA, M.D., MONTREAL, CANADA 133

SOME OBSERVATIONS ON HEART-BLOCK. JAMES G. VAN ZWALUWENBURG, M.D., ANN ARBOR, MICH 141

FRACTURE OF CERVICAL VERTEBRÆ, RESULTING IN HYPOTONIA AND HYPOTHERMIA. HAVEN EMERSON, M.D., NEW YORK 150

THE RELATION BETWEEN ACUTE INFECTIOUS DISEASES AND ARTERIAL LESIONS. CHANNING FROTHINGHAM, JR., M.D., BOSTON 153

THE DIAGNOSTIC IMPORTANCE OF ALBUMIN AND ALBUMOSE IN THE SPUTUM AND THEIR RELATION TO OCCULT BLOOD. EDWARD H. GOODMAN, M.D., PHILADELPHIA 163

EXPERIMENTS WITH THE INTRAVENOUS INJECTION OF SALVARSAN IN ACID SOLUTION. J. AUER, M.D., NEW YORK 169

URINE FORMATION DURING ETHER ANESTHESIA. P. B. HAWK, PH.D., URBANA, ILL. 177

THE LABORATORY DIAGNOSIS OF GENERAL PARESIS. JAMES V. MAY, M.D., BINGHAMTON, N. Y. 183

EDEMA OF THE PIA-ARACHNOID. ITS NATURE, SIGNIFICANCE, RELATIONSHIP TO AND ASSOCIATION WITH DISEASE PROCESSES. CHARLES K. STILLMAN, M.D., NEW YORK 193

A CLINICOPATHOLOGICAL STUDY OF PRIMARY CARCINOMA OF THE LIVER. HOWARD T. KARSNER, M.D., PHILADELPHIA 238

232876

PAGE

BOOK REVIEWS:—DISEASES OF THE HEART AND AORTA. BY ARTHUR D. HIRSCHFELDER, M.D. 262

A TREATISE ON DIAGNOSTIC METHODS OF EXAMINATION. BY DR. HERMANN SAHLI 263

SEPTEMBER, 1911. NUMBER 3

PATHOLOGICAL ANATOMY OF EXOPHTHALMIC GOITER. THE ANATOMICAL AND PHYSIOLOGICAL RELATIONS OF THE THYROID GLAND TO THE DISEASE; THE TREATMENT. DAVID MARINE, M.D., AND C. H. LENHART, M.D., CLEVELAND, OHIO 265

THE SYMPTOMATOLOGY OF TEMPOROSPHENOIDAL TUMORS. FOSTER KENNEDY, M.D., B.CH. (QUEEN'S), NEW YORK 317

FURTHER EXPERIENCE IN THE PREVENTIVE TREATMENT OF RABIES WITH UNCHANGED VIRUS FIXE. FREDERIC PROESCHER, M.D., PITTSBURGH 351

A CONSIDERATION OF SOME CHEMICAL TRANSFORMATIONS OF PROTEINS AND THEIR POSSIBLE BEARING ON PROBLEMS IN PATHOLOGY. FRANK P. UNDERHILL, NEW HAVEN, CONN 356

STUDIES ON WATER-DRINKING. VI. THE ACTIVITY OF THE PANCREATIC FUNCTION UNDER THE INFLUENCE OF COPIOUS AND MODERATE WATER-DRINKING WITH MEALS. P. B. HAWK, PH.D., URBANA, ILL 382

THE IMMEDIATE EFFECT ON THE COMPLEMENT FIXATION TEST FOR LUES OF TREATMENT WITH SALVARSAN (ARSENOBENZOL). AN ANALYSIS OF 225 CASES. CHARLES F. CRAIG, M.D., WASHINGTON, D. C. 395

OCTOBER, 1911. NUMBER 4

THE IMPORTANCE OF TONUS FOR THE MOVEMENTS OF THE ALIMENTARY CANAL. WALTER B. CANNON, M.D., BOSTON 417

BRILL'S SYMPTOM-COMPLEX; TYPHUS FEVER; MANCHURIAN TYPHUS. G. A. FRIEDMAN, M.D., NEW YORK 427

CORRELATION OF CLINICAL PROGRESS WITH THE RESULTS OF IMMUNOLOGICAL STUDIES IN PULMONARY TUBERCULOSIS. ALFRED H. CAULFEILD, M.B., GRAVENHURST, CAN. 440

THE INCOAGULABLE NITROGEN OF PUNCTURE FLUIDS, WITH SPECIAL REFERENCE TO CANCER. A PRELIMINARY NOTE. ROGER S. MORRIS, M.D., ST. LOUIS 457

THE INFLUENCE OF TEMPERATURE ON THE OUTPUT OF THE HEART. HEINRICH F. WOLF, M.D., NEW YORK 463

EXPERIMENTAL CARDIORENAL DISEASE. HENRY A. CHRISTIAN, M.D., R. M. SMITH, M.D., AND I. CHANDLER WALKER, M.D., BOSTON 468

A MODIFICATION OF WOHLGEMUTH'S METHOD FOR THE QUANTITATIVE STUDY OF THE ACTIVITY OF THE PANCREATIC FUNCTION. P. B. HAWK, PH.D., URBANA, ILL. 552

NOVEMBER, 1911. NUMBER 5

CONGENITAL OBLITERATION OF THE BILE-DUCTS. C. P. HOWARD, M.D., IOWA CITY, IOWA, AND S. B. WOLBACH, M.D., BOSTON 557

DUODENAL DIAGNOSIS: X-RAY CONSIDERATIONS. A TECHNIC FOR FLUOROSCOPY. E. H. SKINNER, M.D., KANSAS CITY, MO 574

PAGE

AMEBOID MOVEMENTS IN MACROCYTES AND MEGALOBLASTS. ROGER S. MORRIS, M.D., ST. LOUIS, AND WILLIAM S. THAYER, M.D., BALTIMORE 581

THE EFFECT OF SOME HYDROTHERAPEUTIC PROCEDURES ON THE BLOOD-FLOW IN THE ARM. A. W. HEWLETT, M.D., J. G. VAN ZWALUWENBURG, M.D., MARK MARSHALL, M.D., ANN ARBOR, MICH 591

AN INVESTIGATION OF THE DEPRESSOR ACTION OF PITUITARY EXTRACTS. CAREY P. MCCORD, M.D., ANN ARBOR, MICH 609

OBSERVATIONS ON THE HEMOLYTIC SKIN TEST FOR CANCER. LOUIS M. WARFIELD, M.D., MILWAUKEE, WIS 621

RECOVERY OF A TYPHOID BACILLUS-CARRIER DURING VACCINE TREATMENT. WALTER V. BREM, M.D., LOS ANGELES, CAL., AND F. C. WATSON, M.D., COLON HOSPITAL, CANAL ZONE 630

SUBACUTE LIVER ATROPHY. LINDSAY S. MILNE, M.D., NEW YORK 639

THE DIAGNOSTIC VALUE OF MITOTIC FIGURES IN THE CELLS OF SEROUS EXUDATES. L. F. WARREN, M.D., ANN ARBOR, MICH 648

PERCUSSION SIGNS OF PERSISTENT OR ENLARGED THYMUS. THOMAS R. BOGGS, M.D., BALTIMORE 659

NITROGEN AND FAT METABOLISM AND OTHER FUNCTIONAL TESTS IN A CASE OF CHRONIC PANCREATITIS. HENRY G. BARBOUR, M.D., BALTIMORE 662

THE METABOLISM IN A CASE OF IDIOPATHIC OSTEOPSATHYROSIS. A. BOOKMAN, M.D., NEW YORK 675

THE COAGULATION-TIME OF THE BLOOD AS AFFECTED BY VARIOUS CONDITIONS (TO BE CONTINUED). MYER SOLIS COHEN, M.D., PHILADELPHIA 684

DECEMBER, 1911. NUMBER 6

AN EXPERIMENTAL STUDY OF THE PAIN SENSE IN THE PLEURAL MEMBRANES. JOSEPH A. CAPPS, M.D., CHICAGO 717

THE RELATION OF THE PAPILLARY MUSCLES TO THE MITRAL REGURGITANT MURMURS. W. T. DE SAUTELLE, M.D., AND E. G. GREY, M.D., BALTIMORE 734

TETANUS. E. W. HILL, M.D., COLON, C. Z. 747

A COMPARATIVE INVESTIGATION OF THE EFFECTS AND TOXICITY OF SODIUM SALICYLATES OF NATURAL AND SYNTHETIC ORIGIN. J. A. WADDELL, M.D., CHARLOTTESVILLE, VA. 784

LEUKOCYTIC ENZYMES IN LEUKEMIA IN NEUTRAL MEDIA. ROGER S. MORRIS, M.D., ST. LOUIS, AND THOMAS R. BOGGS, M.D., BALTIMORE 806

THE COAGULATION-TIME OF THE BLOOD AS AFFECTED BY VARIOUS CONDITIONS (CONCLUDED). MYER SOLIS COHEN, M.D., PHILADELPHIA 820

TUMORS OF THE PINEAL BODY. PEARCE BAILEY, M.D., AND SMITH ELY JELLIFFE, M.D., NEW YORK 851

The Archives of Internal Medicine

Vol. VIII JULY, 1911 No. 1

MENINGOCOCCUS ENDOCARDITIS, WITH SEPTICEMIA

ITS BEARING ON THE MODE OF INFECTION IN EPIDEMIC CEREBROSPINAL MENINGITIS

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Meningococcus septicemia was first reported by Gwyn[1] in 1899. The case was one of epidemic meningitis complicated by acute arthritis. The meningococcus was isolated from the spinal fluid, synovial fluid, and the blood. Cochez and Lemaire[2] in 1901 were able to demonstrate the meningococcus in the blood of two meningitis patients. Jakobitz,[3] Martini and Rohde,[4] Lenhartz,[5] Marcovitch,[6] Robinson,[7] and Duval[8] have since made similar reports, the septicemia in all these cases being associated with meningitis. Elser,[9] examining the blood in forty-one cases of cerebrospinal meningitis, found the meningococcus in ten, or about 25 per cent. It has been observed that in most instances where the meningococcus has been found in the circulating blood, the disease has been fatal, and some form of extrameningeal lesion has been present. The endothelial-lined cavities, such as the joints, pleura, pericardium and endocardium have been the sites of these complicating lesions. Duval[8] in his study of meningococcus septicemia makes the statement that no authentic cases are on record in which the meningococcus has produced lesions outside the meninges in the absence of a preexisting meningitis. There is considerable evidence, however, that such infections do occasionally occur. The meningococcus has now been reported several times as occurring in the blood in cases in which there was no evidence whatever of a preexisting or accompanying meningitis.

The earliest case of primary meningococcus septicemia to be reported is that of Salomon,[10] which appeared in 1902. A woman, 32 years old,

1. Gwyn: Bull. Johns Hopkins Hosp., 1899, x, 112.
2. Cochez and Lemaire: Arch. gén. de méd., 1901, i, 573, 667.
3. Jakobitz: München. med. Wchnschr., 1905, lii, 2178.
4. Martini and Rohde: Berl. klin. Wchnschr., 1905, xlii, 997.
5. Lenhartz: Deutsch. Arch. f. klin. Med., 1905, lxxxiv, 81.
6. Marcovitch: Wien. klin. Wchnschr., 1906, xix, 1312.
7. Robinson: Am. Jour. Med. Sc., 1906, cxxxi, 603.
8. Duval: Jour. Med. Research, 1908, xix, 258.
9. Elser: Jour. Med. Research, 1905, xiv, 89.
10. Salomon: Berl. klin. Wchnschr., 1902, xxxix, 1045.

was seized with pain and swellings in her hands, elbows, and knees. These symptoms were followed by chills, fever, and a profuse eruption resembling erythema exudativum. Blood-cultures on agar and in broth yielded the meningococcus. For two months these symptoms continued, the clinical picture being that of a severe sepsis. The patient then developed meningitis, and the cloudy fluid removed by lumbar puncture showed the meningococcus. The patient finally recovered. As there were no symptoms of meningitis during the first two months, it is reasonable to conclude with Salomon that the septicemia preceded the meningitis. The bacteriological notes in this case are very brief. The statement is made that the organism isolated "agreed in all its bacteriological properties with those of the meningococcus," but no cultural or serum reactions are reported.

Andrewes'[11] case, reported in 1906, was that of a physician 50 years old who suddenly developed a hemorrhagic purpura and died a few days later. There were no symptoms of meningitis. Blood-cultures on agar and in broth gave a pure growth of meningococcus. Smears from the blood showed intracellular diplococci in the leukocytes. At the autopsy no meningitis could be found. The organism fermented glucose and maltose and was slightly pathogenic for guinea-pigs.

In 1908 Liebermeister[12] reported the following case: A laborer, aged 59, was admitted to the hospital complaining of pain and stiffness in both shoulders. His symptoms and fever were of the septic type. There was a roseola resembling that of typhoid. There were no signs of meningitis. Several blood-cultures were taken, and all of them yielded the meningococcus. The spinal fluid, however, was normal. After several months' illness the patient recovered without ever having had any symptoms of meningitis. The diplococcus isolated from this case gave the characteristic cultural reactions and was agglutinated by a 1 to 300 dilution of antimeningococcus serum. The patient's serum agglutinated his own organism at a dilution of 1 to 50.

Bovaird[13] has recently reported an interesting case of meningococcus septicemia, occurring in a girl 15 years of age. She was taken suddenly with nausea, vomiting and headache. A few hours later a profuse eruption of irregular purpuric spots appeared over her entire body, and she became stuporous. There was some stiffness of the neck, a positive Kernig, and general hyperesthesia, but the spinal fluid was persistently sterile and free from purulent exudate. Blood cultures gave the meningococcus. The patient developed a severe iridocyclitis, but eventually recovered after receiving several injections of Flexner's antimeningitis serum.

11. Andrewes: Lancet, London, 1906, lxxxiv, 1172.

12. Liebermeister: München. med. Wchnschr., 1908, lv, 1978.

13. Bovaird, David: Meningococcus Septicemia with Sterile Cerebrospinal Fluid, Iridocyclitis; Flexner's Serum; Recovery, THE ARCHIVES INT. MED., 1909, iii, 267.

Netter's[14] case of meningococcus septicemia, reported in 1909, rests on rather inconclusive evidence, but it is at least suspicious. A woman was admitted to the hospital complaining of diarrhea, fever and general malaise. Physical examination showed only a mild bronchitis and some epigastric sensitiveness. There were no signs of meningitis. Spinal fluid was normal. No blood-culture was taken, but the patient's serum agglutinated two strains of meningococcus at a dilution of 1 to 400. The patient's sister had cerebrospinal fever at the time. The diagnosis of meningococcus septicemia was made. She was treated with antimeningitis serum and made a rapid recovery.

Five cases, then, of meningococcus septicemia not associated with meningitis have been reported. In four of these the diagnosis rests on more or less conclusive evidence. Of the five cases only one came to autopsy, that of Andrewes. In this case no focus of infection was recognizable.

In these five cases of primary meningococcus septicemia, no mention is made of any cardiac symptoms suggesting an endocarditis. We have been able, however, to find reports of four cases of meningococcus endocarditis in the literature.

Westenhöffer[15] in his pathological study of twenty-nine cases of epidemic meningitis reported two instances of acute verrucous endocarditis associated with this disease. The first patient, a child 1 year old, had been ill three weeks with epidemic meningitis. At the autopsy there was a suppurative meningitis, bronchopneumonia, acute pharyngitis, and acute rhinitis. On one of the mitral leaflets, small grayish vegetations, the size of peas, occurred.

The second case was that of a woman 21 years old. She was ill only five days. The autopsy showed suppurative meningitis, acute pharyngitis, and acute rhinitis. In the heart both mitral leaflets were the seats of fresh gray vegetations.

No bacteriological report is given in either case. Though the evidence is in favor of a meningococcal origin, it is unfortunate that smears and cultures were not taken from the vegetations.

Weichselbaum and Ghon[16] report the following case: A little girl 9 years old had typical cerebrospinal meningitis. She died after the fifth week, and the autopsy showed meningitis, otitis media, lobar pneumonia, pericarditis, and acute vegetative mitral endocarditis. The meningococcus was recovered from the vegetation. Cultures from the purulent exudate on the brain were sterile, but smears showed Gram-negative diplococci in the leukocytes.

14. Netter: Bull. de l'Acad. de Med., Paris, 1909, lxii, 108.
15. Westenhöffer: Klin. Jahrb., 1906, xv, 657.
16. Weichselbaum and Ghon: Wien. klin. Wchnschr., 1905, xviii, 625.

The case of Warfield and Walker[17] is a particularly interesting one. A negro, 32 years of age, was admitted to the hospital in a delirious condition. For two weeks preceding his admission he had been suffering with headache and cough and later with chills, fever, and delirium. On examination there was herpes, a coated and tremulous tongue, a loud systolic murmur at the apex of the heart, and a temperature of 103 F. Leukocytes 11,000. Patient continued to have chills and to run a septic temperature. At no time were there any symptoms of meningitis. Blood-cultures showed a pure growth of meningococcus. Patient became gradually weaker and finally died one month after admission.

At the autopsy there were acute ulcerative endocarditis of the mitral valve, mitral stenosis, anemic infarcts in spleen and kidneys, and chronic diffuse nephritis. Cultures from the vegetation gave a pure growth of meningococcus. Cultures from the splenic infarct contained streptococcus.

The following is a summary of our case:

REPORT OF CASE

Patient.—A stage carpenter, aged 31, was admitted to the Second Medical Division of the Presbyterian Hospital, June 5, 1910, complaining of headache, pain in left arm and chest, lassitude, and fever. Family history was negative; personal history negative, except for immoderate use of alcohol. Patient gave history of two attacks of rheumatism, the first one fifteen years ago, the second, twelve years ago. He was confined to bed several months during both attacks. He had gonorrhea five years ago. No history of lues.

Present Illness.—Two weeks before admission patient had a sore throat, felt feverish, and noticed some pain and tenderness in right wrist and elbow. Two days later he began to have severe frontal headaches, which continued up to time of admission. He had vomited a number of times and had some diarrhea. In spite of these symptoms, patient continued to work until four days before admission. At that time he began to have a dull pain across the whole anterior chest, which was not increased by the cough that now developed.

Physical Examination.—The patient is a well-nourished man, mentally clear, good color, but much prostrated. Ear-drums normal. Left pupil larger than right, but both react normally. Tonsils moderately enlarged and congested, but without exudate. Neck not stiff. No enlargement of heart made out. Regular action, 100 per minute. Presystolic and systolic murmurs can be heard at the apex. Lungs normal. Abdomen soft. Spleen not felt. No petechiæ, no Kernig, no Babinski. Knee-jerks sluggish. Right ankle somewhat swollen and painful on motion. On the third finger of the right hand the metacarpophalangeal and first interphalangeal joints are swollen, red, and quite tender. Considerable coarse tremor of hands. Temperature 102.5. Pulse 100. Respiration 32. Clinical diagnosis: Rheumatic fever and endocarditis.

Course of Disease.—June 8: The patient's temperature rose to 104.5 and has maintained a level of 102-104.5. Marked tremor of hands has developed. Patient is quite irrational. Symptoms and physical signs otherwise the same. Leukocytes 15,000; 86 per cent. polynuclear leukocytes. The picture is that of an extreme toxemia. The blood-culture taken on the day after admission has been reported sterile. Widal reaction negative.

17. Warfield and Walker: Bull. Ayer Clin. Lab., 1903,-06, i-iii, 81.

June 9: Patient delirious with fairly marked subsultus. Leukocytes 12,000 with 90 per cent. polynuclear leukocytes. No petechiæ. No signs of meningitis.

June 12: Temperature has continued on a level of 103-104. Pulse and respiration have slowly increased, and are now respectively 120-124 and 28-32. Clinically patient has presented a picture of typhoid, except for the absence of rose spots and enlarged spleen. He lies semi-delirious the whole time, having considerable twitching and subsultus. Movements are involuntary, but patient takes fluid greedily. Circulation has kept up well. Blood-culture taken on June 9 gave a pure growth of a Gram-negative diplococcus, which was reported as probably meningococcus. On the basis of that report patient was given 15 c.c. of Flexner's antimeningitis serum subcutaneously without effect. Patient has had no signs of meningitis.

June 14: Patient gradually failing. Temperature, pulse, and respiration are all rising. The blood-culture on June 12 shows same organism found in previous culture. To-day patient received intravenously 15 c.c. of Flexner's serum. Lumbar puncture performed three days ago showed normal fluid. There are now for the first time a few petechial spots, size of pin-heads, just beneath left clavicle.

June 15: Temperature rose to-day to 106. Delirium changed to coma. Some stiffness of legs and neck, thought not to be that of meningitis. Patient died to-night, circulation having steadily failed despite stimulation.

Necropsy.—Performed June 16, sixteen hours after death. Only the most interesting features will be referred to. The body is that of a fairly well-nourished young man, 176 cm. in length. Post-mortem rigidity is present. There is livor mortis in the dependent parts. On opening the abdomen, the liver is found bound to the diaphragm by firm fibrous adhesions. With this exception, the abdominal cavity is negative.

There are old fibrous adhesions in both pleural cavities. The lungs are voluminous and heavy. From their cut surfaces, which are dark red, there oozes considerable blood-tinged frothy fluid.

The pericardial sac has been partially obliterated by fibrous adhesions. The heart, with pericardium attached, weighs 670 gm. and is considerably enlarged. The pericardium is peeled off with difficulty, exposing a rough, ragged surface. The right side of the heart contains a post-mortem blood-clot. The tricuspid valve measures 12.5 cm. in circumference, the pulmonary valve, 8.5 cm. The leaflets of both valves are normal. There is some hypertrophy of the right ventricle.

The mitral valve measures 8.5 cm. in circumference. The two curtains are thickened and fused together so as to form a thick ring. On the auricular surface of the anterior curtain there is a soft cauliflower vegetation, 1.5 cm. in diameter. The base of the vegetation is firmly adherent to the valve leaflet. The aortic leaflets are thickened and pouched. The free borders of the segments are retracted. The left ventricle is considerably enlarged. The papillary muscles are hypertrophied. The musculi pectinati are somewhat flattened. The left ventricular wall measures about 2 cm. in thickness, and has a soft flabby consistence. The musculature is reddish-brown and homogeneous. The coronary arteries are clear.

The spleen is large and soft, weight, 590 gm. The capsule is smooth. The cut surface is dark purplish red, and has a velvety appearance. Considerable pulp comes away with the knife. The markings are indistinct. Along the anterior border there is a sharply defined pinkish-white area, which on section corresponds to the base of an irregular wedge, firm in consistence, and slightly elevated above the surrounding tissue.

The liver is large and rather soft and pliable. Weight, 2,050 gm. The cut surface is pinkish yellow and opaque. Gall-bladder and bile ducts normal.

The pancreas weighs 200 gm. with duodenum attached, and appears normal.

The right kidney weighs 190 gm. The capsule is somewhat adherent. The surface of the kidney is finely granular. The cut surface is cloudy and swollen, the cortex measuring 10 mm. in thickness in some places. At the upper pole,

there is a small pale yellow area surrounded by a narrow zone of red. Section through this area exposes a firm wedge-shaped mass of yellow tissue, surrounded by a dark red zone. The pelvis of the kidney is dilated and contains a large rough stone, which sends off projections into the calyces. The pelvic mucosa is injected, roughened, and covered with mucus. The right ureter is normal.

The left kidney weighs 240 gm. It is finely granular and cloudy like the right. No infarcts occur. Left pelvis and ureter normal.

The suprarenals are normal.

The bladder and prostate are normal.

Nothing of interest is found in the gastro-intestinal tract. The aorta shows no changes. The larynx and trachea are normal.

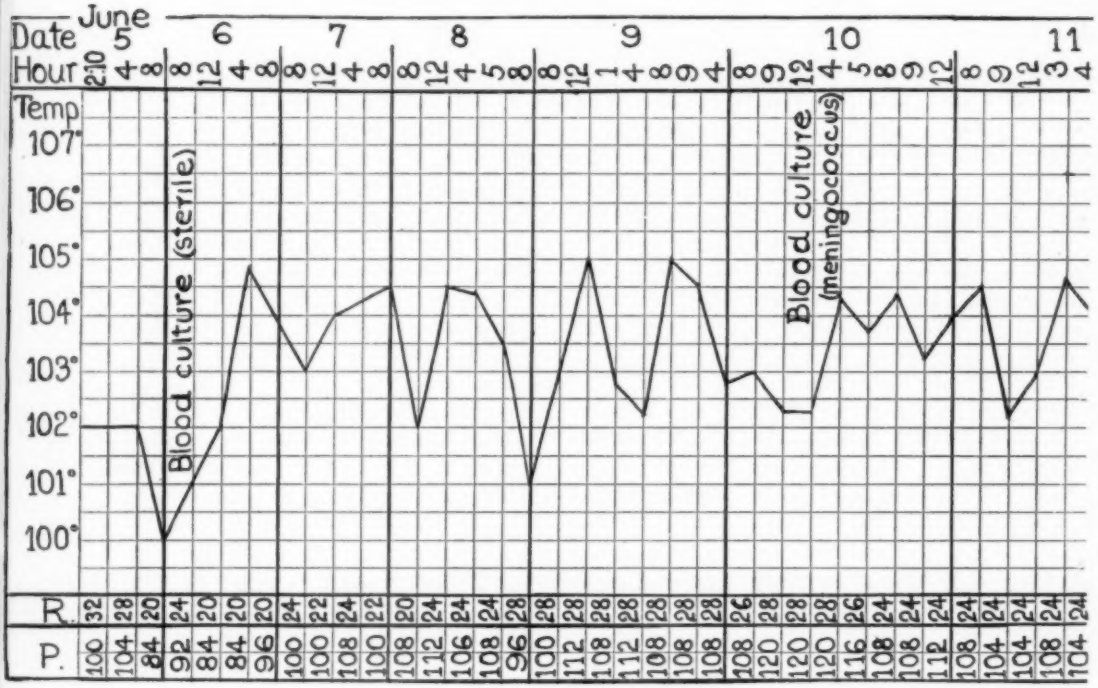


Chart of temperature

The brain weighs 1,450 gm. The dura mater is normal. The cortex is edematous, but translucent. The sulci contain clear serum. The base of the brain is free from exudate. The ventricles are normal. Frontal sections through entire brain show nothing of interest.

Microscopical sections from the organs showed the following: Brain: Sections through the various parts of the cortex, as well as the pons and medulla, show a normal pia-arachnoid. Here and there a few lymphoid and plasma cells occur, but nothing suggestive of an exudate can be made out.

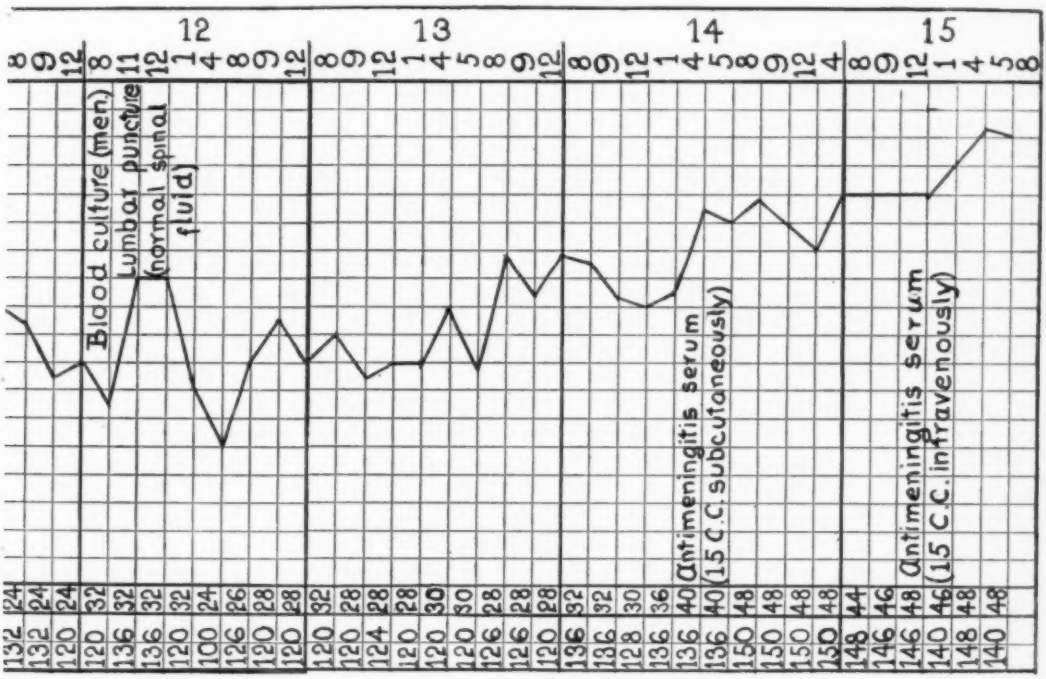
Vegetation on Mitral Valve: The vegetation is composed chiefly of fibrin, which in many places has undergone hyaline necrosis. Toward the periphery, the vegetation contains a large number of polynuclear leukocytes, many of them partially disintegrated.

Kidney: The epithelium of the convoluted tubules is cloudy and granular. At one point in the cortex the tubules and glomeruli have undergone a hyaline necrosis. Around this necrotic area, the veins and capillaries are intensely congested.

Spleen: The sinuses are filled with red blood-cells. There is a large area of coagulation necrosis, throughout which a net-work of fibrin is seen. Just outside the necrotic area, there is a hemorrhagic zone. In several of the larger veins passing through the necrotic focus, fresh mural thrombi occur, some of them occupying half or more of the vessel's lumen.

The liver is cloudy.

Pancreas, suprarenal, lungs and prostate normal.



in case reported.

Heart muscle: There is a slight increase of the interstitial tissue.

Anatomical Diagnosis.—Acute vegetative mitral endocarditis, chronic mitral and aortic endocarditis, mitral stenosis, hypertrophy and dilatation of heart, chronic fibrous pericarditis, chronic interstitial myocarditis, chronic fibrous pleuritis, congestion and edema of the lungs, acute splenic tumor, chronic interstitial nephritis, nephrolithiasis, anemic infarcts in spleen and right kidney, cloudy swelling of viscera.

Bacteriological Examination of the Various Organs.—1. Smears from the vegetation on the mitral valve show red blood-cells, fibrin, and leukocytes. In some of the leukocytes, one to a half dozen pair of Gram-negative diplococci are found. These organisms are biscuit-shaped and show various stages of dissolution. Mor-

phologically, they resemble in every way the diplococcus found in the blood-cultures. A culture taken from the surface of the vegetation shows one colony of *B. coli communis.*

2. Smears from the serous fluid beneath the pia mater show a few endothelial cells. No pus cells or diplococci can be found. Cultures from pia mater give streptococci and colon bacilli.

3. Cultures from liver, spleen, and heart's blood show many colonies of *Bacillus coli communis* and a few colonies of streptococcus.

4. Smears and cultures from the prostate gland show no gonococci.

In order to establish firmly the diagnosis of meningococcus endocarditis it has been necessary to prove two premises: first, that the organism isolated from the patient's blood was a genuine meningococcus; second, that this organism was instrumental in producing the vegetations on the mitral valve.

BACTERIOLOGICAL STUDY OF THE DIPLOCOCCUS

1. Morphology.—The organism isolated from the patient's blood is a small biscuit-shaped diplococcus, which does not retain the Gram stain. Morphologically, it resembles the gonococcus. The diplococci vary considerably in size and many involution forms occur.

2. Cultural Reactions.—Subcultures taken from the original broth flasks showed the following:

On ascitic glucose agar, after twenty-four hours, there appeared a diffuse, grayish, translucent mucoid growth. When some of the growth was removed with a platinum wire, it was seen to have a distinctly viscid quality.

Subcultures in broth, plain agar, blood agar, glucose agar, litmus milk, and Loeffler's blood-serum all remained sterile. By making generous transfers, however, from the ascitic glucose agar culture, growths were obtained on all the serum media, and two weeks later the organism was successfully cultivated on plain and on glucose agar.

TABLE 1.—AGGLUTINATION TESTS

Organism	1-10	1-25	1-50	1-100	1-250	1-500	1-1000	1-2500	1-5000	1-10000	1-15000	Salt Solution Control
Diplococcus, J. S.	+	+	+	+	—	—	—	—	—	—	—	—
Meningococcus "Duval" ..	+	+	+	+	+	+	—	—	—	—	—	—
Meningococcus 250	+	+	+	+	+	+	+	+	+	+	+	—

3. Fermentation Tests.—The organism ferments glucose and maltose, but not lactose or saccharose.

4. Pathogenicity.—A guinea-pig was injected peritoneally with one-fourth of a twenty-four-hour growth of the organism on glucose agar. He appeared sick on the following day, but completely recovered. This test of the organism's pathogenicity was not carried out until two weeks after its first cultivation on culture media.

5. Agglutination and Absorption Tests.—An emulsion of the organism in normal salt solution was prepared from a twenty-four-hour culture on glucose agar. The proportion was 4 mg. of the growth to 1 c.c. of salt solution. Two stock strains of meningococcus were used for controls. The three organisms were tested with the serum from a rabbit highly immunized against the meningococcus. Equal parts of the emulsion and of the variously diluted serum were mixed in small test-tubes and allowed to stand in the incubator at 37 C. for two hours. They were then placed in the ice-box for twenty-two hours. In the positive reactions a flocculent sediment was covered by clear supernatant fluid. In the negative reactions the emulsion remained homogeneous and opalescent. Table 1 shows the results obtained.

Diplococcus J. S., the organism under consideration, was agglutinated by a 1 to 100 dilution of the serum. The first control strain of meningococcus was agglutinated by a 1 to 500 dilution of the serum; the second control, the homologous strain, was agglutinated by a much higher dilution, 1 to 15,000.

In the absorption tests a 1 to 5 dilution of the serum was first mixed with 1 c.c. of an emulsion of the organism, and the mixture incubated at 37 C. for two hours. Then, after thorough centrifugalization, the clear serum was decanted off, and various dilutions of it were tested with the organisms as in the original agglutination tests. In Table 2 the results are seen.

TABLE 2.—ABSORPTION OF MENINGOCOCCUS IMMUNE SERUM

Organism.	Agglutinative Titer with Unabsorbed Serum.	Agglutinative Titer After Absorption with Diplococcus J. S.	Percentage of Agglutinins Lost by Absorption.	Agglutinative Titer After Absorption with Meningococcus 250.	Percentage of Agglutinins Lost by Absorption.
Diplococcus, J. S.....	1-100	1-25	75	1-25	75
Meningococcus, 250 ..	1-15000	1-5000	66.6	1-10000	33.3

The table shows that after absorption of the serum for two hours with diplococcus J. S., the agglutinating power of the serum was considerably reduced for both organisms. In other words, diplococcus J. S. had the power to absorb specific meningococcus agglutinins. Similar reductions in the agglutinative titer of the serum were observed after absorption with its homologous strain, "meningococcus 250."

6. Deviation of Complement.—In addition to the agglutination and absorption tests, we have also tried the deviation of complement test. The hemolytic system devised by Noguchi[18] was employed. The antigen was prepared as follows: a twenty-four-hour growth of the organism was washed from the surface of a glucose agar slant with 1 c.c. of normal salt

18. Noguchi: Jour. Exper. Med., 1909, xi, 392.

solution. The emulsion was well shaken, covered with toluol, and allowed to autolyze over night in the incubator at 37 C. The toluol was then carefully removed, the emulsion centrifugalized, and the clear supernatant fluid pipetted off. For amboceptor we used antimeningococcus horse serum, which was kindly furnished us by Dr. Lamar of the Rockefeller Institute.

There was complete inhibition of hemolysis when 0.01 c.c. of antigen from diplococcus J. S., and 0.05 c.c. of the antimeningococcus serum, were used. With the control strain, inhibition occurred with a slightly smaller quantity of amboceptor, namely 0.02 c.c. These tests were of course controlled with normal horse-serum.

The organism showed all the morphological and cultural characteristics of the meningococcus. It was agglutinated by a 1-to-100 dilution of antimeningococcus serum; finally, it possessed the power of absorbing specific meningococcus agglutinins, and of binding complement with specific antimeningococcus amboceptor. We feel justified therefore in concluding that the organism was a genuine meningococcus.

BACTERIOLOGICAL EXAMINATION OF THE VEGETATIONS

In order to show that the vegetations on the mitral valve were caused by the meningococcus, we studied the smears and culture taken at the autopsy, and in addition have cut sections of the vegetation and stained them for bacteria. The smears showed the characteristic Gram-negative diplococci in the leukocytes. Only one culture was taken from the vegetation, and that showed a single colony of *B. coli communis*.

Examination of sections through the vegetation reveals many polynuclear leukocytes in a partially necrotic network of fibrin. In many of the leukocytes one to a half dozen pair of Gram-negative biscuit-shaped diplococci can be seen. No streptococci can be found in any of the sections of the vegetation.

After having found streptococci in the cultures from the liver, spleen, and heart's blood, it occurred to us that perhaps after all we had been dealing primarily with a streptococcus endocarditis, and that the meningococcus was a secondary invader. A careful study, however, of the smears and sections taken from the vegetations has convinced us that the reverse is true. It has been our experience that in streptococcus endocarditis, no difficulty is found in demonstrating streptococci in and on the vegetation. In the present case, we were unable to demonstrate streptococci in the lesion, but were able to find large numbers of Gram-negative diplococci in the cellular elements of the vegetation.

The streptococcus and colon bacillus were probably both terminal or post-mortem invaders. Neither of these organisms were found in any of the blood-cultures taken. The eighteen hours which elapsed between

the death of the patient and the autopsy gave opportunity for extensive multiplication of the colon bacillus in the blood. Its colonies occurred in large numbers in all the cultures, excepting the one from the vegetation, which contained only one colony of colon bacillus.

The absence of meningococci from all the cultures taken at autopsy may be explained in several ways. The low vitality of the meningococcus, and the fact of its being usually intracellular make it a difficult organism to cultivate under the most favorable circumstances. On several occasions we have seen spinal fluids which contained meningococci in the leukocytes, but from which cultures were persistently sterile. Moreover, Flexner[19] found that in the case of guinea-pigs, killed by intraperitoneal injections of meningococci, if the autopsies were delayed until partial decomposition of the body had set in, or if the dead pigs had been kept for many hours in the refrigerator, the chances of successful cultivation of the meningococcus were greatly reduced. He explains this in the first instance as probably due to the combined action of inflammatory exudate and the products of decomposition; in the second instance, to the low temperature. The fact that in our case the cadaver had been in the mortuary sixteen hours may have been responsible for the negative results obtained.

The second premise may therefore be accepted as proved, namely, that the vegetations were produced by the meningococcus.

DISCUSSION

A critical review of this case and of the four cases reported from the literature reveals nothing definitely characteristic in either the clinical signs or the pathological anatomy of meningococcus endocarditis. Three of the cases were associated with epidemic cerebrospinal meningitis. The other two had no such association. Without bacteriological data, the two cases not accompanied by meningitis might readily have been treated as cases of malignant endocarditis, and even the autopsy would have failed to show the real character of the infection. The cardiac symptoms, the septic temperature, the petechiæ, the prostration, delirium and coma are all seen in streptococcus or pneumococcus endocarditis; the cauliflower vegetations, the infarcts in the kidney and spleen differ in no way from those commonly observed in acute endocarditis of other origin.

It is interesting to note that in our case the first symptom was a sore throat. In the case of Warfield and Walker[17] the disease was ushered in with a cough and yellowish expectoration. According to Osler,[20] all cases of endocarditis may be regarded as secondary to an existing infection. The frequent association of tonsillitis with rheumatism and endocarditis

19. Flexner: Jour. Exper. Med., 1907, ix, 105.
20. Osler: Modern Medicine, 1908, iv, 133.

has led many to the belief that the tonsil is the most common portal of entry for the infecting agent in these diseases. In our case the preexistence of a sore throat and the absence of any other focus of infection would give some ground for suspecting the tonsils, especially when on examination they were enlarged and congested. Unfortunately they were not examined at the autopsy. This suspicion is strengthened somewhat by recalling the fact that the meningococcus is sometimes found in healthy mouths, and is constantly present in the nasopharynx during an attack of epidemic meningitis. Westenhöffer makes the statement that every case of epidemic meningitis is first a case of meningococcus pharyngitis.[21] In twenty-nine autopsies on cases of epidemic meningitis he was able to demonstrate an acute pharyngitis in all of them. The nasopharynx was filled with mucus and the pharyngeal tonsil was invariably swollen and congested. Meyer[22] made a clinical study of thirty-two cases of this disease early in its course, and in twenty-four of them found a well-marked inflammation of the nasopharynx. He was also able to demonstrate inflammation of the pharyngeal tonsil in a majority of cases. Meyer reports one particularly interesting case. The meningococcus was isolated from the secretion in the throat of a patient suffering with angina tonsillaris. On the following day the patient developed a typical meningitis. Von Lingelsheim[23] made an exhaustive bacteriological study of nasal and pharyngeal secretions in epidemic meningitis. He was able to isolate the meningococcus from the nasopharynx of 93.8 per cent. of all cases of meningitis examined. The same organism was found in 15 per cent. of the throats of nurses and attendants. Westenhöffer raises the question whether the nasopharyngeal inflammation could be secondary to the meningitis, and concludes that its appearance so early in the disease, sometimes even preceding it, and the existence of meningococcus "carriers" speak against such a possibility. Kutscher[24] reviews the literature on this subject and concludes that the constant association of pharyngitis with meningitis, and the frequent finding of the meningococcus in the pharynx and nares in cases of meningitis, as well as in those of healthy people, make it in the highest degree probable that the nasopharynx is the portal of entry for the meningococcus.

Although it is generally accepted that the meningococcus gains access to the system by way of the upper respiratory tract, there is some disagreement as to the course taken by the meningococcus in reaching the brain. The earlier writers, notably Weigert, assumed that the infection reached the brain by direct extension upward through the cribriform

21. Westenhöffer: Berl. klin. Wchnschr., 1905, xlii, 737.
22. Meyer: Klin. Jahrb., 1906, xv, 637.
23. Von Lingelsheim: Klin. Jahrb., 1906, xv, 373.
24. Kutscher: In Kolle und Wassermann's Pathogene Microorganismen, 1907, Erster Ergänzungsbd., p. 481.

plate of the ethmoid bone. The nasopharyngeal inflammation, the close proximity of the meninges, and the distribution of the exudate over the base of the brain were the chief arguments brought forward in support of this theory. Westenhöffer,[15] however, in his pathological study of twenty-nine cases, found the ethmoid cells inflamed in only two cases; and in these the changes were slight and apparently secondary to the accompanying rhinitis. In the remaining twenty-seven cases there was nothing to suggest an infection through the cribriform plate.

The investigations of Meyer, Von Lingelsheim, Westenhöffer and others have shown pretty clearly that infection of the meninges, if it does occur by direct extension upward, is effected by an extension from the nasopharynx through the sphenoid bone rather than by an extension from the nasal cavities through the cribriform plate. The constant inflammatory changes in the pharynx have already been referred to; the anterior portions of the nasal cavities are generally free from inflammation. The meningococcus can usually be recovered from the pharynx; rarely from the nose. Westenhöffer[21] believes that epidemic meningitis follows extension of the inflammation through the sphenoidal sinus, and he has formulated an interesting theory in support of it. He quotes the evidence in favor of the hypophysis being a rudimentary sense organ, and observes that the sella turcica almost completely encloses the hypophysis, forming a bony casement about it similar to that about the internal ear. He then refers to the frequent involvement in meningitis of the other cavities connected with the nose and pharynx, and argues that the meningococcal infection, having once involved the sphenoidal sinus, might readily extend through the thin lamina of bone above it. Thirty-four per cent. of Westenhöffer's cases showed an involvement of the sphenoidal sinus. He also found that in patients who died early in the disease, the meningeal exudate was often confined to the region of the hypophysis. He admits, however, that the same type of perihypophysial inflammation may be demonstrated in otogenous, as well as in tuberculous meningitis. Flexner[25] showed that meningococci, when introduced into a low level of the spinal canal of monkeys, distribute themselves in a few hours through the meninges and produce an exudate which accumulates chiefly in the lower spinal meninges and the meninges of the base of the brain. This constant distribution in monkeys of the exudate over the base of the brain led Flexner to "doubt the validity of the reasoning which would ascribe this localization of the inflammation in man to the entrance into the meninges of the infective agent directly through the nasal membrane."

Westenhöffer[15] could find no definite evidence of an infection along the nerve-sheaths, or by way of the lymph-spaces about the carotid arteries. In the few cases in which mild inflammatory changes were encoun-

25. Flexner: Jour. Exper. Med., 1907, ix, 142.

tered, the process was apparently an extension from above downward. He did note a constant enlargement of the cervical lymph-glands with hyperplasia of the chyme centers and infiltration with lymphoid cells.

The occurrence of cases such as the one we have here reported permit a consideration of the hematogenous theory of infection in epidemic meningitis.

Elser and Huntoon,[26] in an exhaustive study of epidemic meningitis, discuss the mode of infection at some length, and summarize the evidence in favor of a hematogenous origin as follows:

> The early appearance of the meningococcus in the blood in a considerable number of cases, the appearance of general sepsis suggested by some patients early in the disease, the lesions in parts far removed from the central nervous system found at the autopsy of individuals who succumbed to the disease within twenty-four hours of its inception, and finally the appearance of characteristic lesions in the eye synchronously with manifestations referable to the central nervous system, all point toward an early generalization of the meningococci, but are not competent to prove that such a general infection actually antedated the meningeal involvement.

The writers just quoted also emphasize the sudden onset of epidemic meningitis, contrasting it in this respect with other forms of meningitis in which a direct infection of the cerebral meninges is reasonably certain, for example, in otogenic or traumatic forms of meningitis. In the latter the onset is usually gradual, beginning apparently as a more or less limited process and extending by degrees over the entire brain. This fact, they reason, is strongly suggestive of a hematogenous infection.

The problem does not lend itself readily to solution by experimental methods. The monkey is the only other animal in which lesions similar to those occurring in man have been produced, but there is a great difference in the degree of their susceptibility. Flexner,[25] studying epidemic meningitis in monkeys, found evidence of extension of the meningeal inflammation into the membranes covering the olfactory lobes and along the dura mater into the ethmoid plate and nasal mucosa. Smears from the nasal mucous membrane showed polynuclear leukocytes containing intracellular diplococci similar in all respects to meningococci. He did not succeed, however, in cultivating the meningococcus from the nose.

Bettencourt and Franca[27] attempted without success to infect monkeys by rubbing the nasal mucous membrane with cotton soaked in a culture of the meningococcus. Negative results have also been obtained when meningococci were injected intravenously into monkeys. It is not surprising that these efforts to infect monkeys outside of the spinal canal have been fruitless. Flexner[25] concluded from his experiments that the quantity of living culture required to cause marked symptoms or death

26. Elser and Huntoon: Jour. Med. Research, 1909, xx, 373.

27. Bettencourt and Franca: Ztschr. f. Hyg. u. Infektionskrankh., 1904, xlvi, 463.

from meningitis in monkeys is enormous if compared with the number of diplococci which probably suffice to produce infection in human beings. If the production of meningitis in monkeys by direct intraspinal injection of meningococci is fraught with such difficulties, it would naturally follow that infection through the blood or lymph, fluids much richer in immune bodies than the spinal fluid, would be still more difficult, or even impossible.

Elser and Huntoon[26] report some interesting and significant experiments which they conducted with a *Streptococcus mucosus*. This organism when injected into the circulating blood of a rabbit, caused some elevation of temperature and loss of weight, but no other symptoms until three days had elapsed. On the fourth day typical symptoms of meningitis developed very suddenly, and the animal died after an illness of only four hours. At the autopsy the brain and cord showed a purulent cerebrospinal meningitis, with a distribution of lesions identical with that found in the epidemic form of meningitis in man. The *Streptococcus mucosus* was recovered from the meningeal exudate. Similar lesions were produced in another rabbit by injecting a pure culture of the same organism in the region of the tonsil. The authors concluded that the organism in question had a special predilection for the meninges of rabbits, analogous to that which the meningococcus shows for the meninges of man. They reasoned that the hematogenous origin of the one spoke strongly for a similar origin in the other.

The evidence therefore at the present time is in favor of a hematogenous mode of infection in epidemic meningitis. It is, of course, possible that infection may occur by either of the routes which have been discussed. Certainly streptococcus, pneumococcus, and staphylococcus meningitis may be either hematogenous or subsequent to direct extension of the infection inward.

The cases of meningococcus endocarditis which we have reported or reviewed have brought out the following interesting facts:

1. The meningococcus, in spite of its affinity for the meninges, may at times become lodged on the endocardium, with the production of an acute vegetative endocarditis. In this respect it resembles most of the other pathogenic bacteria, which, while showing a predilection for some particular organ or tissue, may occasionally produce serious lesions in other parts of the body.

2. The symptoms and pathological anatomy of meningococcus endocarditis correspond to those which characterize malignant endocarditis of streptococcus or pneumococcus origin.

3. Meningococcus endocarditis may or may not be associated with cerebrospinal meningitis.

4. The portal of entry for the organism in meningococcus endocarditis is probably the upper respiratory tract. It is particularly interest-

ing to note that the avenue of infection is the same as that generally accepted as the portal of entry for streptococcus endocarditis on the one hand, and for meningococcus meningitis on the other.

5. The occurrence of primary meningococcus endocarditis with meningococcus septicemia furnishes evidence in favor of a hematogenous mode of infection in epidemic cerebrospinal meningitis.

We wish to thank Dr. Kinnicutt for the privilege of using the clinical notes of this case.

We are also much indebted to Dr. Frank M. Huntoon and to Dr. Richard V. Lamar for their kind suggestions and help in the serological tests.

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A PHYSIOLOGICAL INVESTIGATION OF THE TREATMENT IN HEMOPTYSIS *

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I. INTRODUCTION

It is quite generally conceded that a favorable sequel following the administration of a drug is not a satisfactory test of its efficacy in checking hemoptysis, for it has been proved clinically and experimentally that hemorrhages from the pulmonary vessels often cease with the most surprising promptness. This spontaneous cessation is occasioned through the relatively low pressure reigning in the pulmonary circuit, and the reticular nature of the lung parenchyma, which acts to hasten the clot formation. So efficient are these forces that, in the dog, it has proved impossible to produce a fatal result, even when the main branch to a lobe was cut. Unfortunately, the clinical evidence of fatal issues from hemoptysis indicates that man does not enjoy so certain a protection as the lower animals, a fact to be explained by the slower coagulation of human blood. Hence, the management of pulmonary hemorrhage necessitates the use of such remedies as tend to favor the cessation of bleeding.

As the natural accompaniment of the transition period from empirical therapy to pharmacological experiments, has come the attempt by clinicians to recommend those drugs which so modify the pulmonary circuit that the pressure at the bleeding point lessens; but, in spite of this scientific attitude, one is struck by the apparent lack of unanimity in the choice of drugs.

The perusal of recent text-books on internal medicine indicates mildly the chaotic state that the management of pulmonary hemorrhage is in to-day. Discrepancies such as those cited could be many times reduplicated in the current literature. Admitting that its action is difficult to explain on a physiological basis, Klebs,[1] nevertheless, advises the use of adrenalin (epinephrin) in pulmonary hemorrhage, and Forchheimer[2] speaks of it as "the most valuable of all remedies recommended." This author also advocates the use of ergot, since it has been shown to constrict the pulmonary vessels. On the other hand, Brown[3] writes, "We can hope to gain little by the use of drugs causing a constriction," since "the wall of the bleeding vessel is always diseased." Osler[4] regards the use of ergot as harm-

*This research was carried on during the summer of 1910 at the Research Laboratory of Parke, Davis and Co., Detroit, Mich.

1. Klebs: Tuberculosis, New York, 1909, p. 633.
2. Forchheimer: Prophylaxis and Treatment of Internal Diseases, New York, 1907, p. 156.
3. Brown: Osler's Modern Medicine, Philadelphia, 1910, iii, 404.
4. Osler, W.: Practice of Medicine, Ed. 6, 1906, p. 630.

ful, and Babcock[5] designates ergot preparations as worse than useless on account of their pressure-raising effect on the pulmonary circuit. Kelly[6] also warns against the use of pressure-raising drugs such as ergot, epinephrin, digitalis and strophanthin. In the American edition of Nothnagel's Encyclopedia of Medicine (1905, p. 615), digitalis is recommended because it slows the heart, and this sentiment is faintly echoed by Brown in Osler's "Modern Medicine." Osler and Babcock both discountenance its use, since they believe that the slowing is more than offset by the strengthening action on the heart.

Atropin has been recommended by Babcock on the assumption that the dilatation of the skin vessels draws blood from the pulmonary circuit, while others have condemned its use because of its accelerating action on the heart. Many cardiac depressants, aconite, chloroform and chloral among the number, are frequently recommended in current literature, since they reduce the output of the heart and thus tend to relieve the pressure in the pulmonary circuit. Others condemn their use, fearing to further depress the heart when it is already suffering from anemia.

Authors vary in their faith as to the value of vasodilating drugs, from those who regard them as specific pulmonary hemostatics, to those who take to their use with a certain lukewarmness. For example, F. Hare[7] recommends amyl nitrite on the supposition that it lowers the pulmonary pressure by reducing the pressure in the left auricle. Brown[8] employs it on the supposition that it drains the blood from the lungs into the splanchnic vessels. On the other hand, some, as Babcock, call attention to the fact that the acceleration occasioned may aggravate the bleeding by more than counterbalancing the passive pressure fall.

The causes of these discrepancies are twofold. On the one hand, there has been a tendency among clinical men to regard the control of the pulmonary circulation as a very simple affair, and to consider the effect induced by a single phase of a drug's action to the exclusion of other phases, perhaps no less important. On the other hand, pharmacological experiments have not demonstrated decisively the resultant effect which is induced in the normal pulmonary circuit by the composite actions of a drug, while the modification of drug action during hemorrhage remains practically an uninvestigated territory.

2. *ARGUMENT*

Before attempting an experimental investigation of the influence of drugs in hemoptysis, it is desirable to delineate clearly the criteria which shall determine whether or not a drug's influence will be favorable.

I. THE CONSTRICTOR ACTION ON THE PULMONARY VESSELS

The idea has so long held sway that drugs inducing a constriction can favorably influence hemoptysis that the experimental side of its treatment, to many minds, becomes identified with the investigation of a drug's ability to constrict these vessels. Hemodynamic considerations, however, indicate that such an assumption may not safely be made. In

5. Babcock: Diseases of the Lung, New York, 1907, p. 183.
6. Kelly, A. O. J.: Practice of Medicine, Philadelphia, 1910, p. 541.
7. Hare, F.: Lancet, London, 1904, ii, 942.
8. Brown: Am. Jour. Med. Sc., 1906, cxxxii, 210.

the first place, the action of these agents is limited largely to, or at least predominates in, the smaller vessels, the constriction of which tends to increase the pressure in the pulmonary arteries, and so also to increase the bleeding from this source. In the second place, it must be established that these agents do not act also to increase the minute output of the right heart, for, should they do so, any direct constrictor tendency in the pulmonary vessels might be passively overpowered and thus hemorrhage from the smaller vessels, and even from the veins, be increased. We must conclude, then, that a drug's ability to constrict the pulmonary vessels is not a criterion of its hemostatic value.

II. ABILITY TO LOWER PRESSURE IN THE PULMONARY CIRCUIT

Since the rate of bleeding from the pulmonary vessels is obviously dependent on the pressure within the vessels, as well as on the size of the wound, any decrease in pressure may be regarded as favoring the cessation of hemorrhage. The pulmonary circuit, however, is peculiarly adapted to maintain the normal mean blood-pressure as a minimum standard below which it is rarely permitted to go, even under the most diversified changes in the heart and blood-vessels which are induced by drugs. It is possible to conceive of a combination of physical conditions of such a nature that a hemorrhage could decrease even though the pressure remained unchanged. This would occur provided the resistance ahead of the bleeding point were diminished while the output of the right heart increased just sufficiently to counterbalance this. In such an event, a larger portion of the blood would be directed into the dilated vessels ahead. We may conclude, then, that when a drug causes a lowering of pressure in the pulmonary vessels, that hemorrhage from these vessels must decrease; but the failure of a drug to lower pressure is not of necessity any indication that the bleeding will not be benefited by it. In such cases the flow of blood from a wounded vessel, if caught and continuously measured, is of value in determining directly the effect of drugs.

III. EFFECT ON SYSTEMIC PRESSURE AND RESPIRATION

Obviously the mere fact that a drug lowers the systemic pressure is in no sense an indication that it exerts a similar influence within the pulmonary circuit and hence a discussion of the influence of drugs on the systemic pressure might seem superfluous. From a physiological viewpoint, however, the value of a drug in hemoptysis may not be judged entirely by its ability to reduce the bleeding. The problem which confronts the therapeutist is not as simple as that of the plumber who mends a leaking pipe. The physician must also consider whether the means adopted to stop the bleeding tend to endanger the function of any organ in such a way that it remains permanently disabled or may accelerate a

fatal issue. In previous papers[9] I have dwelt on the necessity of choosing such drugs as do not interfere with the natural compensatory mechanisms that are called into play during hemorrhage. On this basis, the use of pressure-lowering drugs, especially in severe hemorrhages, was discountenanced, since they counteract those mechanisms which strive to maintain the arterial pressure and give an adequate circulation to the brain. So, too, those remedies which dangerously depress an already anemic heart or interfere with the compensatory respiratory mechanisms may become contra-indicated in the severe stages of hemorrhage even though they may favorably influence the bleeding in normal animals.

Summary.—A consideration of the pathological physiology of pulmonary hemorrhage, then, indicates that an investigation of a drug's value in hemoptysis consists, first, in determining its ability during various stages of hemorrhage to reduce the pressure in, or the efflux of blood from, the pulmonary vessels. If it accomplishes this satisfactorily it still remains to be determined whether it tends to relieve the respiratory and vasomotor centers as well as the heart in their compensatory efforts to maintain the circulation. If it is found to antagonize these mechanisms, it becomes physiologically contra-indicated.

3. METHODS AND PROCEDURES

The dogs employed in this research were thoroughly anesthetized by the administration of chloretone intraperitoneally (0.3 gm. per kilo in olive oil). A jugular vein was prepared for introduction of the drug and the carotid pressure was recorded by a mercury or membrane manometer during the rest of the operation. The procedures then varied with the object of the individual experiment. When it was desired to study the effect of a drug on the rate or amplitude of the heart or on the pulmonary circuit independent of modifying respiratory influences, a form of artificial respiration modified from that recently described by Meltzer[10] was used. Through a small tracheal cannula, a small rubber tube or catheter was introduced to the bifurcation of the trachea. The size of the reflux stream which left through the nose or mouth was adjusted, not by adapting the size of the inflow tube to the trachea, as in Meltzer's method, but by tightening a tape ligature placed around the trachea below the opening. By this means the trachea could be narrowed and the lungs inflated to just such an extent that the animal made no attempt at spontaneous breathing. When, in consequence of the loss of blood, the animal resumed respiratory movements, the distention of the lungs was slightly increased or a stream of oxygen substituted for air. This method was found satisfactory except for the tendency of the lungs to become cyanotic, a detail mentioned by Meltzer. This was obviated in the latter experiments by

9. Wiggers: THE ARCHIVES INT. MED., 1909, iii, 139; 1910, v, 438.
10. Meltzer: Jour. Exper. Med., 1909, xi, 622.

substituting for the continuous stream, a briefly interrupted one. This was accomplished by passing the air through a stop-cock so arranged that the period of closure was very brief, during which there occurred, nevertheless, a slight collapse of the lungs, sufficient to prevent the interfering cyanosis, even though the experiment was carried over the greater portion of the afternoon.

With the artificial respiration thus adjusted to the needs of the animal, a cardiometer or cardiograph was applied to the heart, or cannulas were inserted into either the central end of an arterial, or the peripheral end of a venous, branch (for details see former communication[9]). In a num-

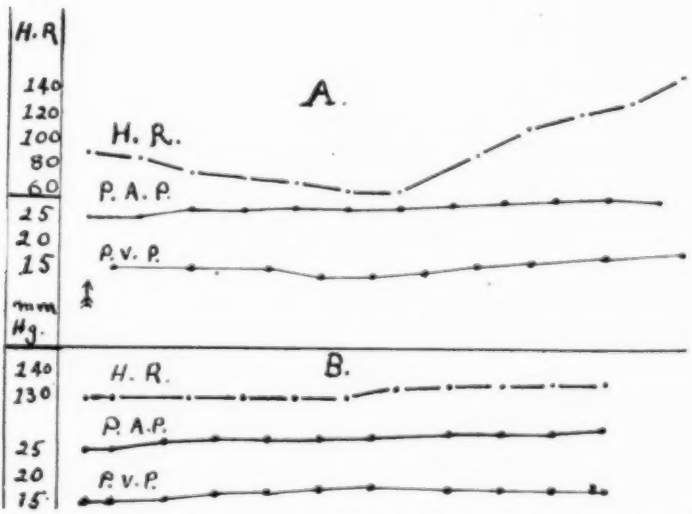

Fig. 1.—Two plots showing the effect of digitalis on heart-rate (H. R.), pulmonary arterial pressure (P. A. P.) and pulmonary venous pressure (P. V. P.); in A, natural respiration experiments, and, B, hemorrhage experiments.

ber of instances the pressure was recorded from a T-cannula and the flow through the lungs thus uninterrupted. These cannulas were connected in different experiments either with a Hürthle manometer alone (which recorded the systolic and diastolic pulmonary pressures and their difference, the pulse-pressure) or simultaneously with a mean pressure manometer much dampened. When the pressure was not decisively altered, the influence of drugs was further studied by leading the blood-flow from one of these cannulas through a short rubber tube to the pan of my drip recording apparatus.[11] In some experiments the pressures in the auricles were also recorded, that of the right, through a long cannula inserted

11. Wiggers: Am. Jour. Physiol., 1908, xxiii, 23.

through the jugular, that of the left, from a cannula in the central end of a pulmonary vein. Experiments in which the above technic was used will be designated as "artificial respiration experiments" in this paper.

Experiments such as these, although fundamental and elucidative, could not by themselves be regarded as determining the value of a drug during hemoptysis. In the first place, many drugs, either directly or through the alteration in systemic pressure, affect the respiratory center, causing changes in rate and depth of respiration which are not without effect on the pulmonary vascular pressure. Accordingly, it became necessary to study the changes occurring during natural respiration. To do this the cardiac appliances and pulmonary cannulas were connected as before. The threaded end of a metal pleural cannula was then fixed into the chest wall by a nut on the inside, after which the thoracic wall was surgically repaired, layer by layer, and thus rendered air-tight, a pro-

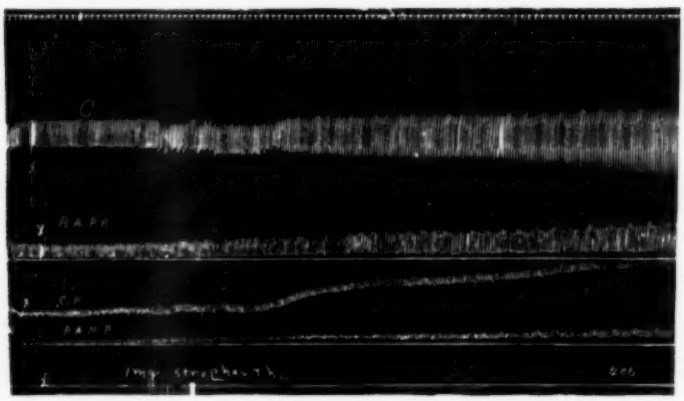

Fig. 2.—Effect of strophanthin (1 mg.) on cardiac output (C), pulmonary arterial pulse pressure (P. A. P. P.), pulmonary arterial mean pressure (P. A. M. P.) and the mean carotid pressure (C. P.). Downstroke of cardiometer tracing in systole.

cedure similar to that described by Fredericq.[12] A negative pressure was then established within the chest through the cannula and this was then connected with a recording tambour. All artificial respiration was then discontinued and the animal resumed natural, quiet respiratory movements, which were recorded by the tambour connecting with the pleural cannula. These experiments will be designated as "natural respiration experiments."

Finally, two other points must be investigated in relation to the choice of drugs in hemoptysis. In the first place, the loss of blood, if fairly

12. Fredericq: Travaux du Lab. de Léon Fredericq, 1880, i, 111.

large, will induce an increase in the rate and depth of respirations, at times amounting to a condition of severe dyspnea. In the second place, as I have before pointed out,[13] the characteristic action of some of our best-known drugs is lost or altered after hemorrhage. Accordingly, the effect of drugs was also determined in experiments in which a condition of dyspnea had been induced by the loss of blood. These experiments will be designated as "hemorrhage experiments."

5. THE EFFECT OF DRUGS ON PULMONARY HEMORRHAGE

Of the many drugs the action of which on the pulmonary circuit was investigated, two classes will be here reported, viz., those which actual experiment has shown to decrease the pressure or hemorrhage in the pulmonary circuit, and those which are most commonly employed in clinical work.

I. DIGITALIS AND ALLIED PREPARATIONS

Recently, Plumier[14] has studied the effect of digitalis on the pulmonary circuit and has also given a review of the literature. From this

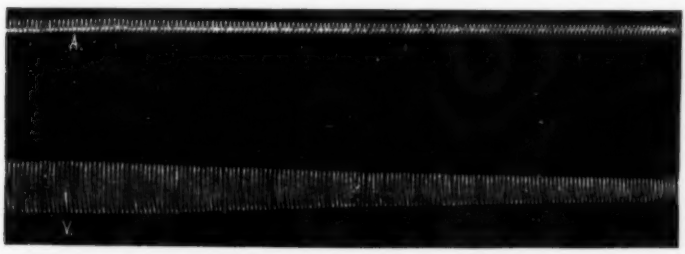

Fig. 3.—Effect of ergotoxin (1.5 mg.) on contractions of auricle (A) and ventricle (V) of a perfused rabbit's heart.

review, it is evident that experimenters are by no means agreed as to whether digitalis causes a rise or a fall or has any effect whatsoever on the pulmonary arterial pressure. The experiments of Plumier above quoted seem to establish clearly, however, that the action of the alcohol contained in the preparations tested was not in all cases adequately considered, and that the pure principles of digitalis induce only a rise of pulmonary arterial pressure. The increase is slight as long as the heart is slowed, but becomes more marked when the slowing is replaced by an acceleration characteristic of digitoxin.

Author's Work.—The results of several experiments confirmed those of Plumier, as far as the effect of digitalis preparations on the pulmonary arterial pressure was concerned, so closely that a detailed investigation of

13. Proc. Soc. Pharmacol. and Exper. Therap., December, 1910.
14. Plumier: Jour. de physiol. et de path. gén., 1905, vii, 455.

this point was deemed unnecessary. Since no attempt had been made to determine the effect of these preparations on the venous pressure, and since the associated question, viz., whether the constricting action on the smaller vessels was overpowered by their action on the heart, remained unanswered, this phase of the drug's action was more extensively entered into. Artificial and natural respiration experiments showed that alcohol-free preparations of digitalis (Infusion, U. S. P., Digitalone, P., D. and Co., Digitalein, Merck) caused in animals with a normal blood-pressure a primary slowing of the heart, followed by a slight acceleration. During the period of slowing, the mean pressure in the pulmonary vein (peripheral end) often remained unchanged, the pulse-pressure due to the slow-

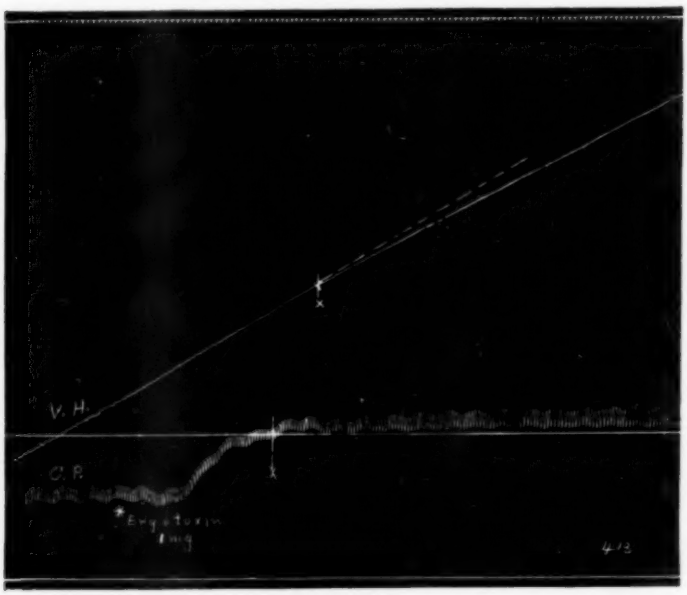

Fig. 4.—Effect of ergotoxin (1 mg.) on carotid pressure (C. P.) and pulmonary venous hemorrhage (V. H.).

ing of the heart became greater and hemorrhage diminished slightly Analysis showed that the constriction induced by digitalis in the pulmonary circuit was great enough to counteract the increased output of the right heart. When the slowing of the heart is gradually replaced by an acceleration, then, however, the local vascular action is overpowered by the augmented minute output of the right heart and the venous pressure rises and hemorrhage increases (Fig. 1, A).

After the loss of a quantity of blood, the actual amount depending on the rate of blood loss, digitalis preparations lose their slowing action on

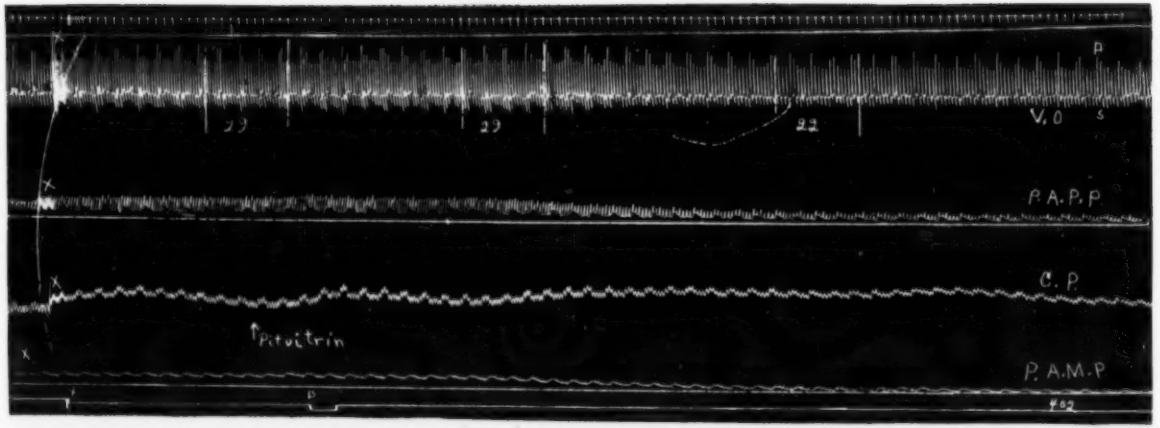

Fig. 5.—Effect of pituitrin (1 c.c.) when heart-rate was not materially slowed, on volume change of ventricles (V. C.), on pulmonary arterial pulse-pressure (P. A. P. P.), on pulmonary arterial mean pressure (P. A. M. P.) and on the carotid pressure (C. P.).

the heart, as I have before pointed out,[13] although the strengthening influence on the heart is maintained. Consequently, the effect of digitalis during hemorrhage differs from the normal in that both the pressure and hemorrhage from the pulmonary veins from the start increase (Fig. 1, B).

Summary.—1. Alcohol-free digitalis preparations cause, in natural and artificial respiration experiments, a rise of arterial pressure and an immediate increase of hemorrhage, owing to the increased minute output of the right ventricle, and the constriction of the pulmonary vessels.

2. They induce a temporary fall in venous pressure and a reduction of venous hemorrhage lasting as long as the heart remains slowed. This is shortly followed by an increased pressure and hemorrhage when the slowing action is lost.

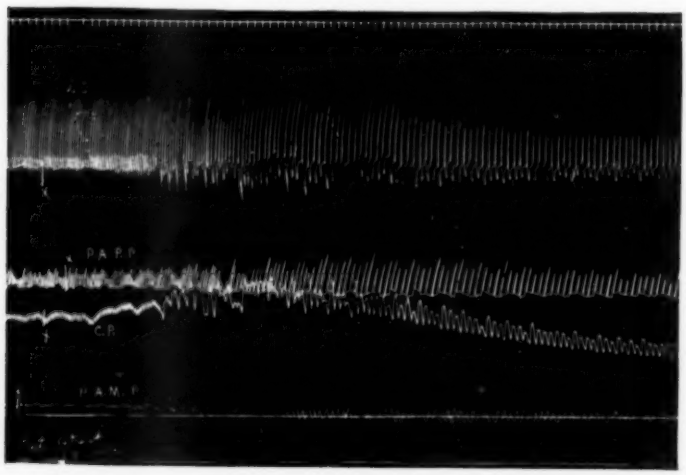

Fig. 6.—Effect of a saline pituitary extract (1 c.c.) when heart was markedly slowed. Lettering same as before. R. A., right auricular pressure.

3. In bleeding animals in which digitalis fails to slow the heart there is only an increase in venous pulmonary pressure and an increase of bleeding from these vessels.

Strophanthin.—Seven animals on which strophanthin was tested showed that this drug differed from digitalis preparations in that, even in normal animals, it failed to slow the heart in the doses tested. The mean carotid pressure and the mean pulmonary arterial pressure simultaneously increased (Fig. 2). Records of the pressure and flow from a pulmonary vein failed to show that strophanthin influenced it in either direction, showing that the constriction of the smaller vessels is just powerful enough to counterbalance the rise of pulmonary arterial pres-

sure. These reactions are sufficient to indicate the lack of beneficial action exerted by strophanthin over pulmonary hemorrhages whether from arteries or veins.

II. ERGOTOXIN

Previous Work.—The experiments of Bradford and Dean,[15] Mellin,[16] Plumier[14] and Dixon[17] are agreed that commercial ergot preparations, such as the fluid extract, ergot aseptic, etc., increase the pulmonary arterial pressure and thus definitely indicate that their intravenous use would be undesirable, at least in hemorrhages from the pulmonary arteries. The cause of the increase of pressure is debatable, however, and the effect on hemorrhages from the pulmonary veins remains an open question. According to Mellin and Plumier, the rise of pulmonary arterial pressure is largely due to a constriction of the pulmonary arterioles.

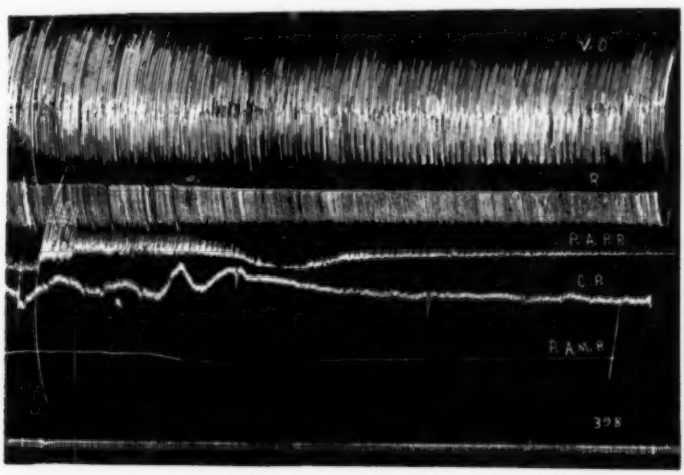

Fig. 7.—Effect of pituitary extract (given at X) on ventricular output (V. O.), on dyspnea (R), on pulmonary arterial pulse pressure (P. A. P. P.), on pulmonary arterial mean pressure (P. A. M. P.), and carotid mean pressure (C. P.).

They maintain that the rise in pressure occurs in spite of a depression of the heart. Dixon, on the other hand, attributes the rise of pulmonary arterial pressure to an increased output of the right ventricle, which he considers powerful enough to overbalance the constriction and cause "the outflow from a branch of a pulmonary vein to be even greater after the administration of ergot than before." These discrepancies are probably

15. Bradford and Dean: Jour. Physiol., 1894, xvi, 86.
16. Mellin: Scand. Arch. f. Physiol., 1904, xv, 147.
17. Dixon: A Manual of Pharmacology, London, 1906.

due, not to the different interpretation of results or to faulty technic, but rather to the use of different preparations of ergot, which are known to vary widely in their content of vascularly active substances. Furthermore, however, it is a well-demonstrated fact that the effect induced by these drugs differs markedly when they are injected intravenously and when they are given subcutaneously or orally. To avoid these difficulties, I limited myself to determining the effect of one of the active principles, ergotoxin, prepared according to the method described by Kraft.[18]

Pharmacology.—Preliminary experiments showed that on the perfused rabbit's heart this preparation decreased the systole and augmented the tonus—the amplitude and output, in consequence, decreasing (Fig. 3). Perfused through an isolated lung, it caused a marked constriction of the pulmonary vessels. Injected into a normally breathing animal, it induced a pronounced and prolonged rise of arterial pressure. The amplitude of cardiac contraction as well as the systolic output were also at first

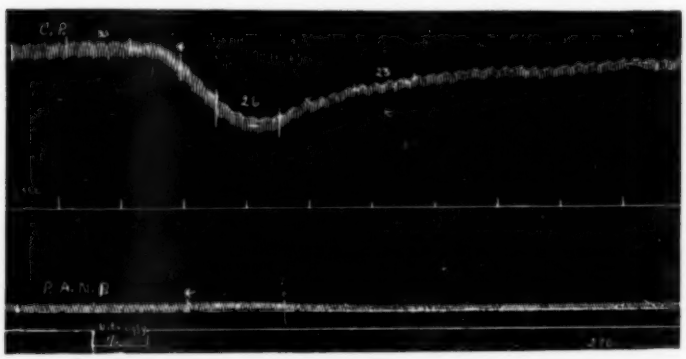

Fig. 8.—Effect of nitroglycerin on carotid pressure and pulmonary arterial mean pressure. Artificial respiration. Lettering same as before.

decreased but later increased. Since ergotoxin exerts a depressing influence on the respiration, in some cases amounting to complete cessation, it is difficult to determine in the intact animal to what extent the subsequent increase in cardiac amplitude may be due to the asphyxial condition.

Effect on the Pulmonary Circuit.—Artificial respiration experiments showed that ergotoxin causes, concomitantly with the rise of carotid pressure and the decrease in the amplitude of the heart, a fall in the systolic and a rise in the diastolic pulmonary arterial pressure. The latter change was due to the effect on the pulmonary arterioles. The effect on the mean pressure and hemorrhage is the resultant of these two actions and, accord-

18. Kraft: Arch. d. Pharm., 1906, ccxliv, 336.

ingly, the hemorrhage slightly decreases or remains unaltered. I have never seen it increase. When the decreased cardiac amplitude is replaced by an increase, the systolic pressure and mean pressure rise. Hemorrhage does not at this time increase, a fact attributable to the coagulating influence of the blood. The changes in the pulmonary veins differed from those observed in the arteries in but one particular. No secondary increase in the mean and systolic pressures was observed when the ventricular beat strengthened, probably because the arterioles remained constricted (Fig. 4).

It may be parenthetically added that these effects on the pulmonary circuit were not obtained with crude ergot preparations.

In natural respiration experiments 1 to 2 mg. of ergotoxin exerted a depressing influence on the respiratory movements causing at times an actual cessation. Under such conditions the decrease in cardiac amplitude

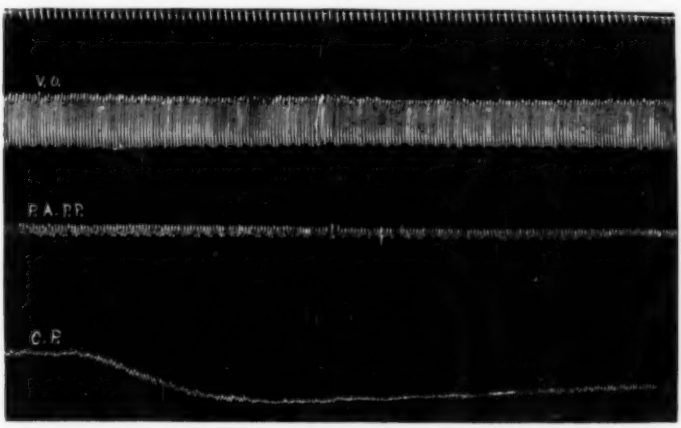

Fig. 9.—Effect of nitroglycerin on the volume of ventricles, on pulmonary arterial pulse-pressure, and carotid pressure. Lettering same as before. After hemorrhage, with artificial respiration.

was replaced by an earlier increase, which was apparently due to an asphyxial effect. Then the systolic and mean pulmonary pressures rose and hemorrhage increased from the arteries but not from the veins.

After the loss of blood the action of ergotoxin on the heart and circulation gradually became less until finally, after severe losses of blood, it exerted no effect whatever. This becomes a serious drawback to the employment of ergotoxin during hemorrhage.

Summary.—1. Ergotoxin temporarily decreases the pulmonary arterial pressure because of its depressant action on the heart. This is followed, especially in normal animals, by an increase due to a secondary augmentation of the heart.

2. The pressure and hemorrhage from the pulmonary veins are permanently decreased, owing to a persistent constriction of the smaller vessels.

3. The action of ergotoxin on the heart and circulation wanes as the loss of blood continues.

III. PITUITARY EXTRACT

Pharmacology.—It is commonly agreed that the posterior lobe of the pituitary gland contains a substance which increases the blood-pressure

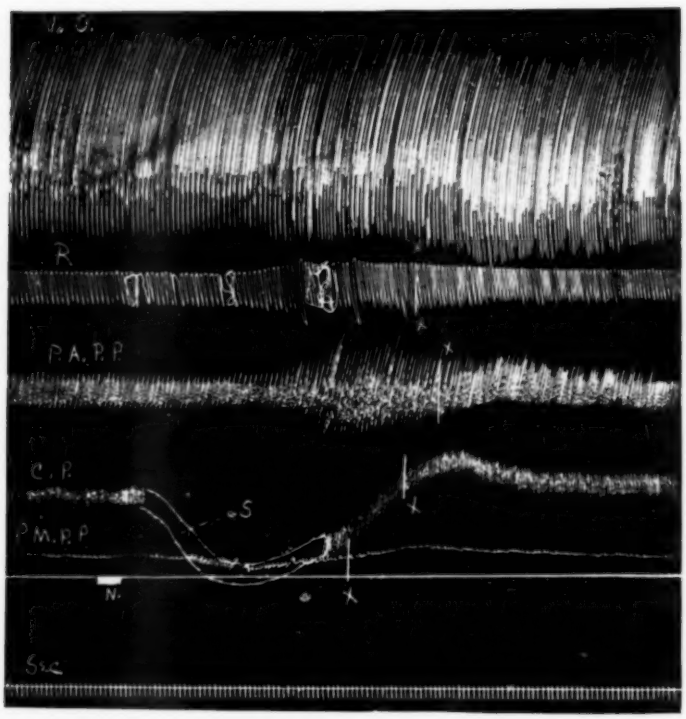

Fig. 10.—Effect of nitroglycerin (1/100 gr.) given at N. Lettering same as before. Natural respiration. X marks relative position of points. S, stylus of carotid manometer caught, and failed to write; therefore the fall of carotid pressure is approximately sketched in. P. M. P. P.—mean pulmonary arterial pressure.

by virtue of a constriction of the peripheral vessels. Recently McCord[19] has shown that this constriction is due to a direct muscular action and that the lung vessels, among those of other organs, are feebly constricted

19. McCord: Unpublished experiments.

by the extract. In the majority of cases it slows the heart and, according to most investigators, increases the amplitude of contraction. Tracings taken from the heart directly show, however, that this assumption is based on inconclusive evidence, and I have pointed out[20] that in cardiographic and oncometer tracings the predominant effect of pituitrin is a depression of the amplitude and a decreased systolic output. In a more extensive series of experiments, McCord[19] has recently shown that this is the chief action of all pituitary extracts although there is at times a preliminary augmentation of very short duration.

Artificial Respiration Experiments.—Intravenous injections of 2 c.c. of pituitary extract (pituitrin or a saline extract of the dried or fresh gland) caused an increase in carotid pressure, the actual rise as well as

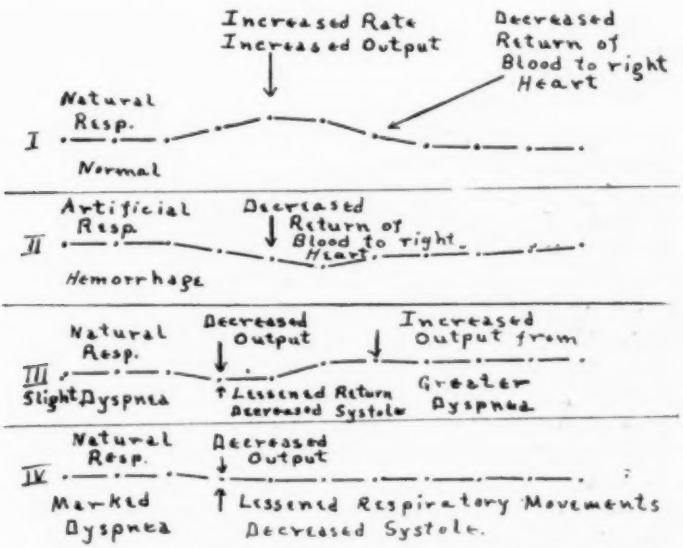

Fig. 11.—Plots illustrating and explaining effects of nitroglycerin and amyl nitrite on pulmonary arterial pressure in normal and bleeding animals.

the duration of which, varied in different animals. At the height of the pressure rise, the output of the ventricle was decreased and in approximately 75 per cent. of cases the heart had slowed (Figs. 5 and 6). Hence, the minute output was decreased whether or not this slowing occurred. Concomitantly with the decreased minute output, the mean pulmonary arterial pressure began to fall. The cause of the fall depended on whether the heart was slowed or not.

20. Wiggers: Am. Jour. Med. Sc., 1911, cxli, 502.

When the heart-rate remained unchanged (Fig. 5) the pulse-pressure in the pulmonary circuit was reduced largely from the drop in the systolic portion. This change, taken together with the cardiometer tracings, indicates, first, that the fall in mean pressure results from a reduced output of the right heart, and, second, that any slight constrictor action on the pulmonary arterioles does not appreciably counteract this change. Hemorrhages from the pulmonary arteries were immediately reduced and with the aid of the coagulating power of the blood were permanently checked.

When the heart was slowed (Fig. 6), the pulmonary pulse-pressure increased from a relatively greater fall of diastolic pressure. This and cardiographic tracings indicate that the fall in mean pressure must be attributed largely to a decrease in the heart rate, for the output of each separate systole is usually greater on account of a more complete filling of the ventricle permitted by the slower rate, but, under these conditions, the mean pressure and hemorrhage were also reduced.

The mean pressure in the peripheral end of the pulmonary vein was decreased in the greatest number of experiments, but in a few it remained unaltered. Hemorrhages decreased with but few exceptions, in which a temporary increase preceded the lessened flow. These results show that the variations of pulmonary arterial pressure are transmitted through the arterioles into the veins and that the lowering of pressure was not neutralized or overpowered by the slight increase in the left auricular pressure occurring in consequence of a weakening of the left heart.

Natural Respiration and Hemorrhage Experiments.—During natural breathing and in the stage of dyspnea from hemorrhage practically the same changes as observed in artificial respiration experiments were obtained. In the latter case the pulmonary arterial and venous pressures decreased, not only from a diminished amplitude and rate of the heart, but also because the respiratory excursions became less vigorous. As seen in Figure 7, this acted to lessen the return of blood to the heart and decreased the diastolic filling.

Summary.—1. Pituitary extract elevates the systemic arterial pressure by virtue of its peripheral constriction and in spite of a weakening of the left heart.

2. The decrease in amplitude of contraction of the right ventricle causes a fall of pressure throughout the pulmonary circuit which neither the weak constricting influence of the drug on these vessels nor the backing up of blood from the left heart counteracts.

3. Pituitary extracts do not directly affect the respiratory center.

4. The actions found to be characteristic of pituitary extracts on normal animals were retained during severe hemorrhages with the exception that it sometimes indirectly lessened the amplitude of dyspneic respiratory movements.

IV. CHLOROFORM AND SIMILAR CARDIAC DEPRESSANTS

Since the depressant action of pituitrin on the heart exerted so favorable a pressure-reduction within the pulmonary circuit, it was deemed advisable to investigate to what extent a similar action could be obtained with other cardiac depressants. Of a number of such drugs which were investigated, chloroform serves as a type and is reported in preference to others, since it has been more specially advocated in pulmonary hemorrhage.[21]

Artificial Respiration Experiments.—From 0.5 to 1 c.c. of chloroform injected intravenously depressed and slowed the heart and lowered the systemic arterial pressure. The decreased minute output of right heart caused the systolic and diastolic pulmonary arterial pressures to decrease and hemorrhage from those vessels to lessen.

Natural Respiration Experiments.—Given by inhalation to normally breathing animals, chloroform, after a momentary gasp, or holding of the breath, causes essentially the same changes in the pulmonary circuit as in artificial respiration experiments. The respiration is somewhat slowed and decreased in amplitude, but this seems of little importance in determining its action on the heart and pulse-pressure. Given during hemorrhage when the respiration has become dyspneic, it slows and weakens the breathing. This causes a fall of pressure throughout the pulmonary circuit without any pronounced effect on the heart, and hemorrhages from the pulmonary vessels may diminish from this effect alone. If the chloroform inhaler is removed and the respirations again become dyspneic, the hemorrhage again increases; but if the inhalations are continued the depression of the heart and the greater lowering of pressure supervene, making the checking of hemorrhage permanent.

Summary.—1. In normal animals, large doses of chloroform cause a fall of pressure within the pulmonary circuit, due to the depression of the heart, aided by the diminished respiration.

2. During dyspnea in hemorrhage, small doses act to lessen the respiratory movements and so decrease the pulmonary pressure and hemorrhage, while large doses act as before through their influence on the heart.

V. NITRITES AND NITROGLYCERIN

Previous Work.—The clinical literature supporting the use of nitrites on the basis that they cause a great fall in pulmonary vascular pressure is so voluminous that even a partial review would carry us far beyond the scope of this paper. It must be confessed that experimental work, on the whole, offers little support to the assumption so generally made that the fall of arterial pressure induced by vasodilator drugs secondarily reduces

21. Fish: 1909, lii, 1918.

the volume of blood and the pressure in the pulmonary circuit. Bradford and Dean[15] found that nitroglycerin as well as amyl nitrite, whether given intravenously or inhaled, caused a marked *rise* in the pulmonary arterial pressure. Wood, Jr.,[22] after restudying the subject, also concluded that nitrites caused a *rise* of pulmonary arterial pressure, but pointed out that sometimes a fall of pulmonary arterial pressure resulted. Mellin[16] recorded the pressure in the pulmonary artery and left auricle simultaneously. The changes after nitrites were variable and slight. Plumier[23] similarly investigated the relative pressure-variations in the pulmonary artery, left auricle and carotid. His published records show a slight rise of pulmonary arterial pressure and, after a short latent period, a still slighter rise of the pressure in the left auricle. Pic and Petitjean[24] again recorded this as the chief reaction, but pointed out that occasionally the pressure remained unaltered, and that once it fell after a brief and insignificant rise.

Of the many who attempted to interpret the results, Plumier apparently carried his work the furthest. He showed that the rise of pressure was *not* due to a constriction of the pulmonary vessels, since (1) the pressure in the left auricle also rose, and (2) the nitrites caused only a dilatation of perfused lungs. Further experiments, in which a dilatation of the systemic vessels was prevented by short-circuiting the blood from the aorta back to the vena cava, showed that no change in pulmonary arterial pressure occurred unless a dose large enough to exert a weakening action on the heart was used, in which case the pulmonary arterial pressure fell. Plumier concludes, therefore, that the rise of pressure following the administration of nitrites in intact animals is due to the fact that a greater transfer of blood through the dilated arterioles to the veins takes place and that thus the right heart receives more to pump out. He fails to show by direct experiment, however, that more blood is returned to the right heart, a fact which may be questioned, first, because the return of blood depends, not only on the arterial dilatation, but also on the pressure in the arteries, and, secondly, because a dilatation of the vessels, as induced by stimulating the depressor nerve, tends to return less blood toward the heart, due to an increased capacity in the splanchnic vessels.

In 1908 and 1909 I performed a series of experiments consisting of forty-three injections of nitrites, to determine the effect (1) on the pulmonary arterial pressure and flow, (2) on the pressure and flow from the peripheral end of a pulmonary vein, and (3) on the left auricular pressure. The apparatus used was the same as before described but all were performed with the chest open and with the rhythmical form of artificial

22. Wood: Am. Jour. Physiol., 1902, vi, 283.
23. Plumier: Jour. de physiol. et de path. gén., 1905, vii, 484.
24. Pic and Petitjean: Compt. rend. Acad. d. sc., 1906, 161; Petitjean: Jour. de physiol. et de path. gén., 1908, x, 405.

respiration commonly in use in laboratories. The results of these experiments showed the same discrepancies among themselves that are evident in the reports of previous investigators with the contrast that the preponderance of cases showed a fall of pressure in the pulmonary circuit, whereas the majority of previous experimenters reported a rise. In many cases both a rise and a fall, as pointed out by Petitjean, were obtained. Since the interpretation and explanation of these varied results was not clear, a report was deferred. They may here be briefly summarized as previous work.

TABLE 1.—PREVIOUS WORK

	Total No. Experiments	Increased	Decreased	No Change
Pulmonary Arterial Pressure	25	5	11	9
Pulmonary Arterial Hemorrhage	6	2	4	0
Pulmonary Venous Pressure	2	1	1	0
Pulmonary Venous Hemorrhage	6	2	4	0
Left Auricular Pressure	7	0	3	4

Present Work.—The work of this investigation concerned itself with the interpretation of these contrary results and a determination of the effects which obtain during hemorrhage.

Artificial Respiration Experiments.—In experiments in which the effects of natural respiration were eliminated, a moderate dose of nitroglycerin caused, in normal animals, a characteristic fall of arterial pressure but synchronously caused a rise of pulmonary arterial and pulmonary venous pressure and hemorrhage. When the systemic pressure began to return to normal, the pulmonary pressures also fell back to normal or occasionally, as shown in Figure 8, below the former level. Cardiographic and cardiometric tracings showed synchronously with the pulmonary change, either no change or an increase in rate of the heart and a slight increase in the amplitude. The rapidity of contraction at times also seemed slightly more rapid. Records of the pressure in the right auricle failed to give any evidence of a greater return of blood to the heart, as claimed by Plumier. As a rule the pressure remained unchanged; a few times it slightly fell.

If the animal had previously lost a quantity of blood (1 per cent. of the body weight or over), the effect induced by the same dose of the drug changed. The arterial pressure fell, the *heart-rate remained unchanged* and its amplitude was often *decreased,* and the systolic output diminished. The pressure throughout the pulmonary circuit, arteries and veins, fell and the pulse pressure decreased. The arterial pressure *remained low,* and the return toward normal was very gradual (Fig. 9).

Natural Respiration Experiments.—The same dose of nitroglycerin or the inhalation of amyl nitrite caused, in normally breathing dogs,

changes similar to those obtained in artificial respiration experiments, viz., a fall in carotid pressure, an increase in the rate of the heart, a very slight augmentation and acceleration of respiration, no change of pressure in the right auricle, or a slight rise in the entire pulmonary circuit. Hemorrhages from the pulmonary arteries and veins increased. The entire effect was, however, of short duration.

If an animal had lost a small quantity of blood so that the respirations were very slightly accelerated and deepened, then the rise of mean pulmonary arterial pressure was preceded by a fall. During the fall the pulmonary systolic pressure rose and the diastolic pressure fell. The cardiac output was decreased. During the rise of the mean pulmonary arterial pressure, the respiration became deeper and more rapid and the cardiac output again increased (Fig. 10).

If the animal had been bled to the stage of excessive dyspnea, the administration of nitrites caused a slight fall in carotid pressure, a depression of respiration to a shallow type, no change in the heart-rate, a decrease in its amplitude and a marked decrease in hemorrhage from the pulmonary vessels, and a fall of pressure here. The carotid pressure, as a rule, did not recover and the experiment soon ended with the total cessation of the respiration.

Interpretation of Results and Their Application to Treatment.—The pharmacological actions of nitrites may be very simply written. They dilate the blood-vessels, and, while large doses weaken the cardiac contractions, small doses have no direct effect. These simple actions call into play a variety of physiological mechanisms which determine the drug's effect on the circulation. The changes in the pulmonary circuit, as outlined above, are so variable and so directly opposed to each other, because, during hemorrhage, other and additional mechanisms are brought into play while some of those normally present are not set into action.

In *normal animals* the dilatation of the peripheral vessels causes a fall in arterial pressure. The consequent decreased blood-supply to the medulla causes a depression of the cardio-inhibitory center, which results in an increase in heart-rate. Furthermore, the amplitude of contraction increases, probably in direct reaction to the lowered arterial pressure. The increase in minute output thus induced aids the return of carotid pressure to normal, while, on the part of the right heart, it causes an elevation of both arterial and venous pulmonary pressures. This simultaneous rise of pressures precludes attributing the rise of pulmonary arterial pressure to a constriction. The rise within the pulmonary circuit occurs in spite of the fact that the pressure in the right auricle remains unchanged or sometimes falls, indicating that the luxus supply of blood normally present in the auricles is still sufficient in the early stages to supply the right ventricle with all the blood it is able to pump out. This does not last long, however, and the deficient supply shows itself in a

return of the pulmonary arterial pressure to normal (or occasionally to slightly below normal) before the heart has resumed its normal rate (Fig. 11, I). Since the respiration in normal animals is little modified by nitrites, these changes occur whether performed with artificial or natural breathing.

During hemorrhage, on the other hand, the heart is already accelerated, owing to a lowered tonus of the cardio-inhibitory center, and can consequently not react by further acceleration. In the second place, the heart seems to be more susceptible to the action of nitrites and is often depressed, as is the case with strong doses in perfusion experiments. In the third place, the luxus supply of blood to the right auricle is less. For these reasons the carotid pressure falls, the output of the right heart lessens, causing a fall of pressure in the pulmonary circuit. *It is apparent that the effects induced in the pulmonary circuit are the direct opposite of those taking place in normal animals* (Fig. 11, II). Since my experiments of two years ago, above quoted, were partly on normal animals and partly on bleeding ones, the discrepancies find an explanation.

This purely circulatory action as determined in artificial respiration experiments is further modified, however, by changes in respiration. If the hemorrhage has been severe enough to have caused a slight acceleration of respiration, then the lowering of arterial pressure by the nitrites will cause a rapid and dyspneic type of breathing. The result is that the venous supply, instead of continuing decreased, is quickly increased by the mechanical effect of the augmented respiration and this increased supply may be sufficient to counteract even a tendency toward a less complete systole, for the minute output becomes increased (Fig. 11, III). Hence the effect on the pulmonary circuit is to cause an increase of pressure and hemorrhage following the decrease.

If the drug is administered during the stage when the respirations are merely increased in rate and amplitude, it causes a marked and often dangerous depression of the respiratory movements. The compensatory influence exerted to return the blood to the chest is then removed and, in consequence, the supply of blood to the heart is reduced. This, together with the weakened systole of the heart, causes a fall of pressure throughout the pulmonary circuit and *is the only time when hemorrhages are diminished by nitrites* (Fig. 11, IV).

We may conclude, then, that the administration of nitrites causes (1) in normally breathing animals, a general increase in pressure throughout the pulmonary circuit, on account of the increased rate and amplitude of the heart; (2) in animals in which the breathing has become slightly accelerated, owing to hemorrhage, also an increase in pressure and hemorrhage from the pulmonary arteries and veins; (3) in the stage when they induce a reduction in the amplitude of respiration, a lowering of pulmonary vascular pressure and a reduction of hemorrhage.

5. SUMMARY AND CONCLUSIONS

The effects of various agents on the respiration, the systemic circulation and on pulmonary pressure and hemorrhage during normal breathing and during the stage of augmented breathing may be summarized as in Table 2, and their application to treatment briefly considered.

TABLE 2.—EFFECT OF VARIOUS AGENTS ON SYSTEMIC PRESSURE, RESPIRATION, PULMONARY ARTERIAL PRESSURE AND HEMORRHAGE, AND PULMONARY VENOUS PRESSURE AND HEMORRHAGE

Drugs	Systemic Pressure	Respiration	Pulmonary Arterial Pressure and Hemorrhage	Pulmonary Venous Pressure and Hemorrhage
Digitalis—				
Normal	+	0	+	(—)+
Hemorrhage	+	0	+	+
Strophanthin—				
Normal, Hemorrhage	+	0	+	+
Ergotoxin—				
Normal	+	—	—+	—
Hemorrhage	0	—	0	0
Pituitary—				
Normal	+	0	— or (+)—	—
Hemorrhage	+	—	—	—
Chloroform—				
Hemorrhage, Normal	—	—	—	—
Nitrites—				
Normal	—	0	+	+
Hemorrhage early	—	+	(—)+	(—)+
late	—	—	—	—

Early in the course of hemoptysis, when the breathing has not altered except for an occasional cough, one is dealing practically with a normal subject, and the object of paramount importance is to promptly reduce the bleeding by such drugs as lower the pressure within the pulmonary circuit. Investigation shows (1) that this cannot be accomplished by vasomotor drugs such as nitroglycerin or nitrites, and (2) that cardiac depressants, such as chloroform and pituitary extracts, must be resorted to.

If hemorrhage has continued until the heart is very rapid and the respirations accelerated, deep and forcible, it is an indication (1) that the heart and blood-vessels no longer react in a typical manner to certain drugs, and (2) that the anemia of the cerebral centers is being felt. During this stage it is important that the blood-supply of the brain be not reduced by the drugs which check hemoptysis. Hence, the drug that combines an ability to elevate systemic arterial pressure and simultaneously to lower that in the pulmonary circuit is the ideal physiological agent to employ during this stage. In the entire gamut of drugs investigated, pituitary extract is the only one that possesses this fortunate combination of actions.

POSTANESTHETIC GLYCOSURIA*

P. B. HAWK
URBANA ILL.

INTRODUCTION

It has long been recognized that reducing material appears in the urine following the induction of chloroform narcosis in man or the lower animals. At the time the data from the first experiments made by me were reported[1] it was not generally known, so far as I am aware, that any considerable glycosuria could be induced in lower animals by subjecting them to ether anesthesia.[2]

Among the earlier investigators of the chloroform glycosuria were Hégar and Kaltenbach.[3] They observed that the urine following chloroform anesthesia possessed reducing power and asserted that this reducing power was not due to the production of sugar but to the presence in the urine of chloroform which was excreted in part through the kidneys. A few years later Zweifel[4] found that the urine of the fetus had reducing power after the mother had been anesthetized. This investigator maintained that the reduction was not due to sugar, but to chloroform which had passed from the mother into the fetal circulation. Von Mering[5] made a similar observation and in addition noted that the urine was levorotatory. In 1878 Pavy[6] observed the reducing power of the urine from twenty subjects of chloroform narcosis and showed the reducing material to be glucose. Kappeler,[7] on the contrary, was able to demonstrate the reducing property in the urine in but one case in twenty. Goodwin[8] in observations on clinical cases is said to have noted glycosuria in only one case out of sixty-five, whereas under ether anesthesia, sugar was demon-

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1. Hawk: Proceedings of the American Physiological Society, Am. Jour. Physiol., 1904, x, p. 37.

2. The presence of reducing material in urines following ether anesthesia was independently observed by Professor Gies and Mr. White at the College of Physicians and Surgeons (New York) before they were aware of my findings (Hawk and Gies: Am. Jour. Physiol., 1904, xi, 227).

3. Hégar and Kaltenbach: Virchow's Arch. f. path. Anat., 1870, xlix, 437.

4. Zweifel: Berl. klin. Wchnschr., 1874, xi, 245.

5. Von Mering: Quoted by Zweifel (see note 4).

6. Pavy: Quoted by Vidal (Thèse de Paris, 1897).

7. Kappeler: Anæsthetica, Stuttgart, 1880.

8. Goodwin: Therapeutic Gazette.

strated in the urine of two subjects out of twenty-eight. In every instance of glycosuria the reducing power of the urine disappeared after the first day.

Zeller[9] observed a strong reduction in the urine of a dog after subjecting the animal to chloroform anesthesia, and further verified the finding of von Mering as to the presence of a levorotatory substance. He concluded that there existed in the urine an organic chlorin body, formed from the conjugate glycuronates of the urine and trichlormethyl alcohol, which was produced from the chloroform by oxidation. Kulz[10] also noted the levorotation of the urine after operations but he attributed it to the presence of conjugate glycuronates which had been formed from the absorbed phenol. Sabarth[11] asserts that there is a true chloroform glycosuria and explains it as arising from imperfect respiratory exchange during the induction of the anesthesia. Drapier[12] manipulated the urine properly to remove all reducing substances other than sugar and in this way showed the existence of a real chloroform glycosuria. This glycosuria was inconstant and according to Drapier was due to hepatic irritation and asphyxic glycemia.

One of the most interesting series of experiments on chloroform glycosuria was made by Kast.[13] He came to the conclusion that postoperative glycosuria occurs even when no chloroform is used and that the reducing property of the urine following chloroform narcosis is not, therefore, due entirely to the presence of chloroform. Kast was of the opinion that the reduction was due principally to the presence of an organic chlorin combination such as Zeller described. He was, however, unable to demonstrate the levorotation observed by Zeller and by von Mering, and mentions the probability that the substance having this levorotatory power may have been removed by his manipulation of the solution in the process of clarification.

Vidal's[14] experiments on the influence of chloroform narcosis on the reducing power of the urine are very interesting. Out of forty-one clinical cases, the urine of thirty-five showed reduction after anesthesia or increased reduction in cases in which the urine passed just previous to the induction of narcosis possessed reducing power. Three out of four experiments on dogs showed a similar result. Vidal repeated some of Kast's experiments and came to the conclusion that the postanesthetic reducing power of the urine was not due to free chloroform, since the reducing power persisted even after the urine had had an air current

9. Zeller: Ztschr. f. physiol. Chem., 1883-84, viii, 70.
10. Kulz: Centralbl. f. d. med. Wissensch., 1888, xix, 337.
11. Sabarth: Das Chloroform, Würzburg, 1886.
12. Drapier: Influence des anæsthétiques sur la nutrition, 1886.
13. Kast: Berl. klin. Wchnschr., 1888, xxv, 377.
14. Vidal: Thèse de Paris, 1897.

passed through it for six hours. Chloroform added to urine was removed entirely in a similar length of time. He further found, on evaporating the urine and dissolving the residue in water, that the reducing power of the aqueous solution was as strong as that possessed by the original urine. Vidal concluded that the reducing substance was not glucose, since he was never able to obtain phenylglucosazone crystals, although in control experiments he was able to obtain positive results with a 0.1 per cent. solution of glucose. The levorotation mentioned by previous authors he was unable to demonstrate. He proved by suitable tests that the reduction was not due to uric acid and finally was able to show a rough relation between the reducing power of the urine and the amount of organic chlorin present.

Seegen[15] investigated the sugar content of the blood of the hepatic vein before and after chloroform anesthesia, and reached the conclusion that such narcosis had an inhibitory effect on the formation of sugar in the liver. He also tested the urine of four persons after chloroform anesthesia[16] and was unable to detect a trace of sugar. Lépine and Boulud[17] state that the lessening of the glycolytic power shown by Seegen occurs only when the narcosis is prolonged and that when the inhalation of the anesthetic is limited to a few minutes there is a hyperglycemia, as has been shown by Garnier and Lambert.[18] Noel Paton[19] has shown that in the living animal as well as in the excised liver, chloroform hastens the conversion of glycogen into dextrose. He found ether to possess a similar although less marked action. In later experiments Paton[20] showed that chloroform did not have so great an accelerating action on amylolysis in the liver after treating the organ with alcohol as it possessed immediately after death. Patein[21] was unable to demonstrate any reducing power in the urine from several clinical cases following chloroform narcosis.

Previous to the preliminary report of my investigation, already mentioned, I could find no record of any series of experiments on the reducing power of the urine of dogs after ether narcosis. Subsequently, however, Seelig[22] made a series of observations on clinical cases and on dogs and rabbits. He found that glycosuria occurred in every instance in his observations on lower animals, but was unable to demonstrate such a condition in connection with his clinical cases even after long-continued ether narcosis. He found the glycosuria to be very pronounced, analysis

15. Seegen: Centralbl. f. d. med. Wissensch., 1887, xxv, 577.
16. Seegen: Wien. med. Wchnschr., 1888 xxxviii, 953.
17. Lépine and Boulud: Arch. int. de pharmacol., 1905, xv, 359.
18. Garnier and Lambert: Quoted by Lépine and Boulud (see note 17).
19. Paton: Phil. Tr. Roy. Soc., London, 1894, Part I, 233.
20. Paton: Jour. Physiol., 1899, xxiv, 36.
21. Patein: Thèse pour le doctorat en Médécine, Paris, 1888.
22. Seelig: Arch. f. exper. Path. u. Pharmak., 1905, lii, 481.

of the urine indicating as much as 10 per cent. sugar in some cases. Seelig asserts that glycosuria is less pronounced in dogs after long-continued carbohydrate feeding than in such animals maintained on a meat diet. In an article recently published Tuckett[23] makes the statement that "Seelig was the first to show that ether produces a distinct, though small glycosuria in meat-fed dogs." Inasmuch as my preliminary report was made in 1904 whereas Seelig's article was published in 1905 it is apparent that Tuckett's statement is incorrect. Seelig refers to the experiments of Reynoso,[24] who, in the examination of urine from clinical cases, claims to have found sugar in every instance after ether anesthesia. Röhricht[25] examined the urine of patients after operations of various orders, 100 cases being reported. Of this number only twelve showed spontaneous glycosuria, the highest sugar content as determined by polarimeter being 1 per cent. He was of the opinion that the tendency toward glycosuria after ether increased with the age of the subject, although his data do not substantiate this theory. Röhricht made other experiments in which operations were performed under local anesthesia, and was unable to demonstrate any traces of glycosuria. Out of six experiments on the influence of ether anesthesia unaccompanied by operation three showed glycosuria. Carlson and Ryan[26] have reported the occurrence of postanesthetic glycosuria in cats. This observation was made in connection with an investigation having for its purpose the study of the dextrose content of the saliva. The finding of reducing matter in human urine following the ingestion of alcohol as reported by Georg[27] is also of interest in connection with the present glycosuria studies.

DISCUSSION OF THE EXPERIMENTS ON WELL-NOURISHED ANIMALS

The experiments under consideration were conducted on dogs, some of which were the same as those utilized in experiments already reported.[28] Some of the tests were on dogs which were in nitrogen equilibrium, whereas others were made on the fasting organism. The animals were permitted to urinate normally, careful watch being kept in order that accurate record might be secured of each individual urine fraction voided after anesthesia. To this end, immediately after the urine was voided, the urine receptacle was removed and a fresh one substituted, while the volume, reaction and specific gravity of the urine were determined and a

23. Tuckett: Jour. Physiol., 1910, xli, 88.
24. Reynoso: Compt rend. Soc. de biol., 1851, xxxiii, 416 and 606.
25. Röhricht: Zentralbl. für Chirurgie, 1905, xxxii, 1010.
26. Carlson and Ryan: Am. Jour. Physiol., 1908, xxi, 301.
27. Georg: Wien klin. Wchnschr., 1900, xiii, 370.
28. Hawk: Jour. Biol. Chem., 1908, iv, 321; Jour. Med. Research, 1908, new series, xiii, 203.

qualitative test for sugar[29] was made. The urine fraction was then transferred to a small bottle, properly labeled, some powdered thymol added and the sample retained for quantitative examination. In every instance the urine of the animal was shown to be sugar-free before the administration of the anesthetic. Squibb's ether was employed. The anesthesia periods ranged in length from one-half hour to six and three-quarter hours.

The data from the experiments will be found tabulated in Tables 1 to 6. In the first series of experiments, Dog. 1, a bitch weighing slightly over 6 kg., was employed. She served as a subject in three experiments, being under the influence of the anesthetic five times, the periods varying in length from one hour to three hours. The first test was one hour in duration, which was followed about nine hours later by the voiding of 100 c.c. of urine containing 3.26 per cent. of dextrose. The urine collected for twenty-two hours from this time contained a trace of reducing matter but subsequent fractions gave negative tests. The second experiment on this animal was one in which anesthesia was induced for a period of two hours. This test was followed in about six and one-half hours by the voiding of a fraction of urine having a volume of 74 c.c. and containing 5.21 per cent. of dextrose. It will be observed that the first urination after the induction of anesthesia occurred about two and one-half hours sooner when the period of narcosis was two hours in length than when the period was but a single hour in duration. The volume of urine voided was only about 75 per cent. as great, however, while its sugar content was much higher, i. e., 5.21 per cent. as against 3.26 per cent. The total amount of sugar excreted as a result of one hour's narcosis was 3.26 gm., whereas 3.91 gm. were excreted as a result of the two-hour period.

The third test on this animal was a composite experiment in which the dog was subjected to ether anesthesia on each of three consecutive days, the periods being one, two and three hours in length respectively. The first fraction voided after the first anesthesia period (one hour) of the series was one of 39 c.c. which appeared about six hours after the administration of the anesthetic had ceased. This urine specimen contained 3.17 per cent. of sugar. The two-hour period of anesthesia was followed in about four and one-half hours by the voiding of a fraction of urine 52 c.c. in volume and possessing a sugar content of 1.32 per cent.

29. Throughout the experiments Fehling's qualitative and quantitative tests were used and any reducing action was ascribed to dextrose. However, there were instances when it seemed apparent that there was present reducing matter other than dextrose. In every case of extensive reduction, however, I was able to form the dextrosazone. In some instances the conjugate glycuronate content was considerably increased. There seemed to be no uniformity in the nature of the reducing factor under all circumstances. This question will be studied further.

Finally the three hours' narcosis gave rise in less than two hours to a urine flow aggregating 91 c.c. which contained 3.96 per cent. of dextrose.

From an examination of the data from the five periods of anesthesia to which Dog 1 was subjected it will be noted that there is a somewhat definite relationship between the length of the anesthesia period and the

TABLE 1.—POSTANESTHETIC GLYCOSURIA IN DOG 1.

EXPERIMENT 1.—ETHER ANESTHESIA INDUCED FOR ONE HOUR

	Urine Fraction — Voided					Sugar Content
No.	Hour	Length of Time After End of Narcosis Hrs.	Min.	Volume c.c.	Specific Gravity	%
...	.....	..	..	..	.....	..
...	.....	..	..	..	.....	..
...	.....	..	..	..	.....	..
...	.....	..	..	..	.....	..
1	7:00 p. m.	8	53	100	1020	3.26
2	Between 7 p. m.	8	53			
	and 8 a. m.	to				
		21	53	185	1020	Trace

EXPERIMENT 2.—ETHER ANESTHESIA INDUCED FOR TWO HOURS

1	6:30 p. m.	6	29	74	1030	5.21
2	Between 6:30 p. m.	6	29			
	and 8 a. m.	to				
		19	59	134	1017	0.04
3	11:25 a. m.	23	24	78	1016	Faint Trace

EXPERIMENT 3.—ETHER ANESTHESIA INDUCED FOR PERIODS OF ONE, TWO AND THREE HOURS ON THREE CONSECUTIVE DAYS

ETHER ANESTHESIA INDUCED FOR ONE HOUR

1	4:30 p. m.	5	58	39	1042	3.17
2	Between 6 p. m.	7	28			
	and 7:30 p. m.	to				
		8	58	84	1010	Trace

ETHER ANESTHESIA INDUCED FOR TWO HOURS

1	4:30 p. m.	4	26	52	1026	1.32
2	Between 4:30 p. m.	4	26			
	and 8 a. m.	to				
		19	56	180	1023	Trace

ETHER ANESTHESIA INDUCED FOR THREE HOURS

1	2:00 p. m.	1	55	91	1028	3.96
2	4:45 p. m.	4	40	66	1016	0.43
3	Between 4:45 p. m.	4	40			
	21st & 5 p. m. 22d	to				
		28	55	221	1022	Faint Trace

percentage of dextrose present in the first fraction of urine subsequently voided. For example, in Experiment 1, in which narcosis was induced for one hour, the sugar content of the urine fraction was 3.26 per cent. whereas the value was 5.21 per cent. for the urine first voided after the two-hour period. Again in the composite test (No. 3) the concentration of the urinary dextrose was 3.17 per cent. after one hour's anesthesia and

the higher value of 3.96 per cent. after the three-hour period. The relation is not absolutely uniform, inasmuch as the dextrose concentration following the two-hour period of narcosis was only 1.32 per cent. The sugar data from the last two stages of the composite test, however, cannot logically be compared with individual experiments, inasmuch as the organism was not permitted to recover from the first anesthesia before being subjected to its influence a second and third time. Nevertheless, the data will permit the assertion that there was in general a relation between the length of the anesthesia period and the concentration of the urinary dextrose. The longer the period of narcosis the larger was the percentage of sugar in the urine.

Taking into consideration the five individual anesthesia periods of Dog 1, an interesting point is observed in regard to the length of time intervening between the time the anesthetic was discontinued and the appearance of the first urine fraction. A rather definite relationship between the length of anesthesia and the percentage of urinary dextrose

TABLE 2.—POSTANESTHETIC GLYCOSURIA IN DOG 2

EXPERIMENT 4.—ETHER ANESTHESIA INDUCED FOR HALF AN HOUR

Urine Fraction						Sugar
No.	Voided			Volume	Specific	Content
...	Hour	Length of Time After End of Narcosis		c.c.	Gravity	%
...	.....	Hrs.	Min.	..	.....	..
1	4:30 p. m.	7	45	40	1038	2.14
2	Between 4:30 p. m. and 8 a. m.	7	45			
		to				
		23	15	314	1015	Trace
3	5:00 p. m.	32	15	46	1026	Trace

has just been discussed. There is no such relationship as that to be noted in this connection, however. For example, when the data from the two one-hour anesthesia periods are compared, it is seen, in Experiment 1, that the first urine was voided about nine hours after the close of the administration of the anesthetic, whereas this period was only six hours when the ether was given a second time for a period of equal length. Further, by making a similar comparison for the two-hour periods of anesthesia, the "latent period" is seen to be six and one-half hours in the first instance and four and one-half hours in the second. Finally, it will be observed that the first fraction of urine voided after the three-hour period of anesthesia followed very quickly, there being a latent period of less than two hours.

From the above discussion it is apparent that the length of the period intervening between the end of the administration of the anesthetic and the voiding of the first fraction of urine was entirely independent of the length of the anesthesia period. In the series of tests on this animal the

latent period shortened with each successive narcosis, being nine hours after the first administration of the ether and two hours following the fifth administration. This point is demonstrated very clearly in Table 1.

The fourth experiment was made on a bitch weighing about 7.5 kg. (Dog 2). She was subjected to a single anesthesia period thirty minutes

TABLE 3.—POSTANESTHETIC GLYCOSURIA IN DOG 3

EXPERIMENT 5.—ETHER ANESTHESIA INDUCED FOR ONE HOUR

No.	Urine Fraction — Voided — Hour	Length of Time After End of Narcosis Hrs.	Min.	Volume c.c.	Specific Gravity	Sugar Content %
...	.....	.....		..	.....	..
1	11:30 a. m.	1	15	36	1030	6.94
2	4:45 p. m.	6	30	58	1034	0.07
3	Between 4:45 p. m. and 8 a. m.	6 to 21	30 45	300	1021	Trace
4	2:00 p. m.	27	45	70	1016	Trace

EXPERIMENT 6.—ETHER ANESTHESIA INDUCED FOR TWO HOURS

1	11:20 a. m.		15	6	1030	None
2	12:30 p. m.	1	25	14	1031	5.21
3	2:30 p. m.	3	25	30	1033	0.22
4	4:30 p. m.	5	25	39	1039	0.04
5	Between 6:00 p. m. and 8:00 a. m.	6 to 20	55 55	340	1020	Trace

EXPERIMENT 7.—ETHER ANESTHESIA INDUCED FOR FOUR AND ONE-HALF HOURS

1	Passed during narcosis	..	..	18	1024	None
2	2:15 p. m.	..	47	106	1037	3.66
3	3:30 p. m.	2	2	21	1018	0.06
4	4:30 p. m.	3	2	14	1036	0.06
5	7:00 p. m.	5	32	94	1032	0.33
6	11:20 p. m.	9	52	72	1039	0.15
7	Between Midnight and 6:00 a. m.	15	52	151	1018	0.13
8	9:00 a. m.	18	52	58	1015	0.09
9	4:00 p. m.	22	52	36	1024	Trace

EXPERIMENT 8.—ETHER ANESTHESIA INDUCED FOR ONE HOUR

1	12:45 p. m.	1	50	34	1039	3.76
2	4:15 p. m.	5	25	40	1039	0.10
3	Between 6:00 p. m. and 8:00 a. m.	7 to 21	10 10	367	1017	Trace

in length (Table 2). This period was followed after seven and three-quarter hours by the voiding of a urine fraction which possessed a volume of 40 c.c. and contained 2.14 per cent. of dextrose. This was the shortest anesthesia period investigated, and the urine fraction also contained the lowest percentage of dextrose observed during the investigation in the

initial urine fraction. The urine voided through a period of thirty-two hours still contained a trace of dextrose. The latent period in the case of this animal was seven and three-quarter hours, which is fairly comparable to the latent period of nine hours following the initial anesthesia of Dog 1. The anesthesia period, however, in the latter case was one hour as against half an hour in the case of Dog 2.

Next followed a series of four experiments (5 to 8) on Dog 3, an animal weighing about 10 kg. Data from this series of tests are given in Table 3. In the first experiment (5) the period of narcosis was one hour. The first urine subsequently voided appeared in an hour and a quarter. It was only 36 c.c. in volume and contained 6.94 per cent. of sugar. These data are strikingly different from those obtained under similar circumstances from Dog 1 in Experiment 1. In this instance, it will be remembered that the period elapsing between the end of the

TABLE 4.—POSTANESTHETIC GLYCOSURIA IN DOG 5

EXPERIMENT 9.—ETHER ANESTHESIA INDUCED FOR ONE HOUR

Urine Fraction						Sugar
No.	Voided	Length of Time After End of Narcosis		Volume c.c.	Specific Gravity	Content %
...	Hour	Hrs.	Min.	..	.....	..
...	.....			..	.....	..
...	.....			..	.....	..
...	.....			..	.....	..
...	.....			..	.....	..
1	4:50 p. m.	3	35	70	1024	2.73
2	7:45 p. m.	6	30	11	1040	0.56
3	12:00 m.	10	45	385	1031	Trace
4	5:00 p. m.	15	45	24	1020	Trace

anesthesia period and the appearance of the first fraction of urine was nine hours, the volume of the fraction was 100 c.c. and its sugar concentration 3.26 per cent. It is evident therefore that the administration of ether for a one-hour period to each of Dogs 1 and 3 was followed by latent periods of nine hours and an hour and a quarter, urine volumes of 100 c.c. and 36 c.c. and sugar concentrations of 3.26 per cent. and 6.94 per cent. respectively. These data furnish a very striking illustration of the variation in the reaction of different organisms to the same anesthetic administered through periods of equal length.

The second experiment on Dog 3 embraced an anesthesia period of two hours. The initial fraction of urine in this instance, was voided only fifteen minutes after the end of the period. It was but 6 c.c. in volume, and contained no sugar, although its specific gravity (1.030) indicated a high concentration of solids. [In this connection attention may be called to the fact that there was no relation, in any of the tests, between the specific gravity of the urine fraction and its sugar concentration. In the case in point, for example, a urine containing no sugar possessed a specific gravity of 1.030 whereas in Experiment 5 the urine containing 6.94 per

cent. of sugar possessed a similar specific gravity. The lack of relationship is further accentuated when it is noted that the urine fraction voided immediately after the one with this high sugar concentration (6.94 per cent.) possessed a higher specific gravity (1.034) although containing but a trace (i. e., 0.07 per cent.) of sugar.] In the case of this experiment (6) the reducing matter in the urine persisted for a period of about twenty-one hours as against twenty-eight hours in Experiment 5. The great bulk of the sugar, however, was excreted in the second fraction of

TABLE 5.—POSTANESTHETIC GLYCOSURIA IN A FASTING DOG (No. 14)

EXPERIMENT 10.—ANIMAL ALLOWED WATER

Day of Fast	Urine Fraction No.	Voided	Length of Time After End of Narcosis Hrs. Min.		Volume c.c.	Specific Gravity	Sugar Content %
...	...	Hour			..	.....	..
...	...	.....			..	.....	..
...	...	.....			..	.....	..
...	...	.....			..	.....	..
...	...	.....			..	.....	..
		ETHER ANESTHESIA INDUCED FOR ONE HOUR (9:30-10:30 A. M.)					
18	1	7:50 p. m.	9	20	33	1041	0.52
..	2	Between 10:00 p. m. and 8:00 a. m.	11 to 21	20 20	64	1038	Trace
		ETHER ANESTHESIA INDUCED FOR TWO HOURS (8:20-10:20 A. M.)					
22	1	6:45 p. m.	8	25	19	1046	Trace
..	2	Between 10:30 p. m. and 8:00 a. m.	12 to 21	10 40	47	1043	None
		ETHER ANESTHESIA INDUCED FOR TWO HOURS (8:30-10:30 A. M.)					
27	1	9:45 p. m.	11	15	14	1055	None
.	2	Between 9:45 p. m. and 8:00 a. m.	11 to 21	15 30	39	1049	None

urine, which was voided about an hour and a half after the anesthetic had ceased to be administered. This fraction was only 14 c.c. in volume and contained 5.21 per cent. of dextrose. An interesting fact may be observed in connection with the sugar data from Experiments 2 and 6. In these tests two dogs were subjected to ether anesthesia for periods of two hours each and the first urine subsequently passed contained in each instance 5.21 per cent. of dextrose. (In this connection no consideration is given to the 6 c.c. fraction in Experiment 6.) This may be more or less of an accidental finding, inasmuch as the body weights of the dogs were different as were also the volumes of the urine fractions and the total output of sugar. Nevertheless, the uniformity in percentage of sugar is worthy of consideration.

The third experiment on Dog 3 was Experiment 7 in which the term of anesthesia was four and one-half hours. Here for the first time during

the investigation urine was voided spontaneously during narcosis. The volume of this fraction was 18 c.c. and it was sugar-free. The second fraction of urine was voided forty-seven minutes after the ether was discontinued. This fraction possessed a volume of 106 c.c. and contained 3.66 per cent. of dextrose. This experiment differed from all others in the number of urine fractions which were voided during the period of

TABLE 6.—POSTANESTHETIC GLYCOSURIA IN A FASTING DOG (No. 8)

EXPERIMENT 11.—ANIMAL ALLOWED WATER

Day of Fast	Urine Fraction No.	Voided: Hour	Length of Time After End of Narcosis: Hrs.	Min.	Volume c.c.	Specific Gravity	Sugar Content %
	...	...	.....		..	.....	..
	...	...	.....		..	.....	..
	...	...	.....		..	.....	..
	...	...	.....		..	.....	..
	...	...	.....		..	.....	..
	ETHER ANESTHESIA INDUCED FOR ONE HOUR (8:20-9:20 A. M.)						
8	1	5:30 p. m.	8	10	13	1044	0.43
..	2	Between 10:00 p. m. and 8:00 a. m.	12	40 to 22	40	25	1037 Trace
	ETHER ANESTHESIA INDUCED FOR ONE HOUR (8:10-9:10 A. M.)						
9	1	6:40 p. m.	9	30	10	1052	0.25
..	2	Between 10:30 p. m. and 8:15 a. m.	13	20 to 23	5	19	1041 None
	ETHER ANESTHESIA INDUCED FOR TWO HOURS (8:10-10:10 A. M.)						
14	1	8:20 p. m.	10	10	9	1057	Trace
..	2	Between 10:00 p. m. and 7:40 a. m.	11	50 to 21	30	16	1050 None
	ETHER ANESTHESIA INDUCED FOR ONE HOUR (8:30-9:30 A. M.)						
26	1	Between 11:20 p. m. and 8:05 a. m.	13	50 to 22	35	5	1062 None
	ETHER ANESTHESIA INDUCED FOR SIX AND THREE-FOURTHS HOURS (9:20 A. M. TO 4:05 P. M.)						
27	1	Removed from bladder after death.	..	..	3	1068	None

glycosuria. There were eight such fractions as against two, three or four fractions in the other experiments. The glycosuria persisted for about twenty-three hours in this experiment.

Experiment 8 was the final one of the series on Dog 3. The animal had already been subjected to ether anesthesia for periods of one, two and four and one-half hours. It was now determined to submit the beast again to a final one-hour period in order to determine whether the dog

would react differently from the way it did at the original administration of the anesthetic. The first fraction of urine subsequently voided was one of 34 c.c. which appeared one hour and fifty minutes after anesthesia. Its sugar value was 3.76 per cent. A comparison of the data from this experiment with that of Experiment 5 will be of interest. When this animal (Dog 3) was first subjected to ether anesthesia for a period of one hour, the initial urine fraction subsequently voided was one of 36 c.c. which appeared after an interval of an hour and a quarter and contained 6.94 per cent. of sugar. During the intermediate period the beast was subjected to two additional experiments, one in which the narcosis period was two hours and a second test in which ether was administered for a period of four and one-half hours. Finally the animal was again subjected to ether anesthesia for a one-hour period. As a result of this final test the first urine fraction was voided in one hour and fifty minutes as against an hour and a quarter at the initial test. The volume of the fraction was 34 c.c. as against 36 c.c., whereas the percentage of sugar present had decreased from 6.94 per cent. to 3.76 per cent. Hence it may be contended that the anesthesia periods of two and four and one-half hours respectively were instrumental in causing a slight lengthening of the latent period and an increase in the intensity of the glycosuria following the final one-hour anesthesia period.

The last experiment (9) on the well-nourished animals was made with Dog 5 as subject. This animal was a bitch and weighed about 7 kg. She was subjected to but a single anesthesia period, the length of which was one hour. Data from this experiment are given in Table 4. It will be observed that the urine first voided after narcosis appeared after the lapse of about three and one-half hours. This fraction had a volume of 70 c.c. and contained 2.73 per cent. of sugar. The second fraction was voided about three hours later and contained only 0.56 per cent. of sugar. The lack of relationship between the specific gravity of the urine fractions and their sugar concentration is very clearly demonstrated in this experiment. The fraction containing 2.73 per cent. of sugar had a specific gravity of 1.024, whereas the following fraction showed an increase of specific gravity to 1.040, this increased density being accompanied by a decrease from 2.73 per cent. to 0.56 per cent. in the dextrose content. The glycosuria persisted for a period of about sixteen hours in the case of this animal.

A comparison of the data from the different experiments in which the anesthesia periods were one hour in duration will be of interest. There were two such tests on each of Dogs 1 and 3, the data being given in Tables 1 and 3. The fifth and final study of this character is the experiment just reviewed in which Dog 5 was subject. In these five tests on three different dogs the length of time elapsing between the end of anesthesia and the voiding of the first urine specimen varied from one

hour and fifteen minutes to nine hours. The volumes of these initial urine fractions ranged from 34 c.c. to 100 c.c., while the sugar content varied from 2.73 per cent. to 6.94 per cent. The term of glycosuria persisted from a minimum of nine hours to a maximum of twenty-seven and three-quarter hours. We thus see that there was no uniformity between the types of the reaction in the five tests of the influence of a one-hour anesthesia period.

Taking into consideration the experimental data just reviewed I should interpret these data as indicating that the glycosuria following the induction of ether anesthesia in well-nourished dogs is due primarily to the effect of the anesthetic in stimulating the transformation of the glycogen of the organism into dextrose. It is entirely possible that dyspnea was a contributing factor inasmuch as Araki,[30] Lepine and Boulud,[31] Micha and Reynoso,[32] and Underhill[33] have all demonstrated that lack of oxygen may give rise to hyperglycemia or glycosuria. That different organisms will react differently under the influence of similar anesthesia periods is clearly shown, among other things, by the wide variations in the intensity of the glycosuria produced. In this connection attention should be called to the variation of the urinary sugar concentration from 2.73 per cent. to 6.94 per cent. in the initial fractions of urine following one hour's anesthesia in five different instances on three different dogs. Mention should also be made of the variation in the persistence of the glycosuria under different conditions. It should also be remembered that with certain dogs the latent period became progressively shorter as the number of anesthesia periods to which the animal was subjected was increased. There was no uniform relationship between the specific gravity of the urine voided after anesthesia and its sugar concentration.

Reference may be made to some interesting findings on postanesthetic glycosuria which were observed in connection with some experiments conducted primarily for the purpose of studying the urine formation during ether narcosis. In these experiments the animals were placed under ether; then cannulas were inserted in the ureters and the course of the urine flow observed for periods of from ten to twelve hours.[34] The volume of urine collected in the sub-periods of one hour was so small as to preclude the possibility of making tests on each individual fraction. However, the urine fractions from Experiments 12 and 14 were each made into a composite sample and these were then subjected to a quantitative examination. The sample from Experiment 12 in which the dog was under ether for ten hours and twenty minutes contained 5.29 per

30. Araki: Ztschr. f. physiol. Chem., 1891, xv, 335.
31. Lepine and Boulud: Compt. rend. de l'Acad. Sc., 1902, cxxxiv, 1341.
32. Micha and Reynoso: ibid 1853, xxxvi, 230.
33. Underhill: Jour. Biol. Chem., 1905, i, 113.
34. The Archives Int. Med., 1911 (to be published).

cent. of sugar. The urine from Experiment 14 in which the period of anesthesia was eleven hours and fourteen minutes, contained 6.32 per cent. of dextrose.

DISCUSSION OF THE EXPERIMENTS ON FASTING ANIMALS

Dogs were used as the subjects in these experiments and in every instance were allowed water *ad libitum*. The first fasting test (Experiment 10) was made on Dog 14 and the resulting data will be found in Table 5. In this experiment the animal was subjected to three periods of anesthesia. The first period was one hour in length, the ether being administered to the animal during the forenoon of the eighteenth day of fast. The second period of narcosis was two hours in length, the experiment being made on the twenty-second day of fast. The third and final test was also one of two hours, the anesthetic being administered on the twenty-seventh fasting day. As was to have been expected, the data from these experiments are entirely different from those already considered in connection with the well-nourished dogs. For example, the one-hour period of anesthesia was followed in a little over nine hours by the voiding of a fraction of urine containing but 0.52 per cent. of dextrose. The sugar concentration obtained with the well-fed dogs under similar conditions ranged from 2.73 per cent. to 6.94 per cent. In other words, the ether produced only one-thirteenth to one-fifth as pronounced a glycosuria in the fasting organism as in the organisms of the well-nourished animals. The persistence of the glycosuria was very similar in the two cases.

The second test, also on Dog 14, occurred on the twenty-second day of fast and embraced a two-hour period of anesthesia. The administration of the ether was followed in about eight and one-half hours by the voiding of a fraction of urine which showed only a trace of reducing matter. After an interval of five days, i. e., on the twenty-seventh day of fasting, the dog was again subjected to the anesthetic for a second period of two hours. On this occasion, for the first time during the tests, the ether failed to produce glycosuria. The first fraction of urine, which was passed about eleven hours after the discontinuance of the administration of the anesthetic, contained no reducing matter. It possessed a specific gravity of 1.055, however, thus showing a higher density than that of any other urine fraction voided by this animal.

The second series of fasting tests was made on Dog 8. These are embraced in Experiment 11 and the data from the series are given in Table 6. This animal, in common with the dog used in Experiment 10, was allowed free access to water. During the course of this test the influence of five anesthesia periods was studied, there being three one-hour periods, one two-hour period and one period which was six and three-quarter hours in length. The first anesthesia period occurred on the

eighth day of the fast and was one hour long. This was followed in about eight hours by the voiding of a small fraction of urine (13 c.c.) which contained 0.43 per cent. of dextrose. The data in this regard are very uniform with those from the initial anesthetization of Dog 14, in that the percentage of sugar in the former experiment was 0.52 per cent. as against 0.43 per cent. in the test under consideration. On the following day, the ninth of fasting, the animal was again subjected to the administration of the anesthetic for a period of one hour. This too was followed by a very slight glycosuria, which was represented by a urinary sugar concentration of only 0.25 per cent. The third anesthesia period was tested on the fourteenth fasting day and was productive of a mere trace of reducing matter in the urine. This period was followed on the twenty-sixth day of fast by a one-hour period of narcosis. Here for the second time in the fasting studies it was impossible to demonstrate any subsequent glycosuria.

By referring to the proper tables it will be observed that the failure to demonstrate glycosuria in the first instance followed a two-hour period of anesthesia on the twenty-seventh day of the fast, whereas the second failure to demonstrate the postanesthetic glycosuria occurred after a one-hour narcosis period induced on the twenty-sixth day of the fast. This uniformity is of interest although perhaps void of much significance. The final test on Dog 8 was an anesthesia period of six and three-quarter hours, this being the maximum period employed in the course of these studies. The organism having failed to react to the influence of the previous anesthesia period of one hour it was determined to employ this protracted period in order to determine more definitely the possibility of producing postanesthetic glycosuria in an organism in the advanced stages of fasting. The data as tabulated indicate that there was no glycosuria. The dog was killed under anesthesia and the urine (3 c.c.) present in the bladder gave a negative reduction test. The specific gravity of this urine was 1.068, thus showing a higher density than was possessed by any other urine examined during these experiments.

When the data from the two fasting dogs are compared, the uniformity in the two instances is very evident. In each case the glycosuria following ether anesthesia was very slight as compared with that following anesthesia of well-nourished dogs. In each experiment there was a gradual decrease in the sugar concentration of the urine at each successive anesthetization. This is shown very nicely in Experiment 11, in which 0.43 per cent. of dextrose was present after the first anesthesia period, 0.25 per cent. after the second, a trace after the third and none after the fourth period. No such progressive decrease was observed in the case of the well-fed animals. In each fasting experiment, moreover, the ether failed to produce glycosuria when the fasting period was suffi-

ciently prolonged, the length of the period being practically the same in each experiment, i. e., from twenty-six to twenty-seven days.

As I have already mentioned, I am inclined to interpret these data as indicating that the postanesthetic glycosuria observed in the experiments reported was due primarily to the effect of the ether in stimulating the transformation of glycogen into sugar. This deduction is further strengthened from the fact that in the experiments in which fasting animals were anesthetized there was a much less pronounced glycosuria in the early days of the fast than had been previously observed in the case of the normally nourished animals, and further that when the fasting period was sufficiently prolonged there were no signs of glycosuria when the animals were subjected to long periods of ether narcosis. No experiments were made in which the glycogen content of the liver was determined after ether anesthesia and a comparison made between the data thus obtained and the data for the liver glycogen of control animals;[35] but in view of the findings of Paton[20] and of Vidal[14] relating chiefly to chloroform it seems probable that the glycosuria observed to follow the induction of ether anesthesia was due primarily to the transformation of liver glycogen into dextrose. Vidal's experiments on rabbits are of particular interest in this connection. This investigator made four experiments, in each of which he took two rabbits of approximately the same body weight, subjected them to fasting and on the fifth day placed one of them under the influence of chloroform for fifteen minutes. Twenty-four hours later both the anesthetized and the control animals were killed and the glycogen content of the liver and muscles determined. In every instance the glycogen content of the liver and muscles of the anesthetized animals was much less than the glycogen content of the liver and muscles of the control animals. In one experiment the relation between the data for the content of liver glycogen under the two conditions was 2.9:0.96, thus indicating that the glycogen value after narcosis was only 27.7 per cent. of the normal value. An observation made by Underhill[35] is of interest in connection with our findings in the case of fasting dogs. This observer found when dogs were fasted to "extreme emaciation," thus greatly reducing the glycogen store, that no hyperglycemia followed the application of piperidin, a drug which induced this condition in well-nourished animals.

I do not maintain that the non-appearance of glycosuria following the administration of ether to dogs in the advanced stages of fasting indicates that the livers of such animals were glycogen-free at the time the experiment was performed. In fact, the consensus of opinion would be distinctly against such a view, inasmuch as it has frequently been shown that the livers of dogs, even after prolonged fasting, still contain

35. Observations of this nature are contemplated.

glycogen. I would offer the following interpretation of the data. The well-nourished organism contains a comparatively large quantity of glycogen deposited principally in the liver and muscles. The entrance of such a factor as ether anesthesia so alters the customary processes as to be followed by the transformation of a portion of this stored glycogen into dextrose and its subsequent appearance in the urine. There is, however, a limit to the intensity of this anesthesia stimulation and the accompanying glycosuria. A certain amount of the glycogen may be considered as a reserve supply to be drawn on only in times of great emergency. All glycogen other than this reserve glycogen, in the case of the fasting organism, has been nearly depleted through the ordinary demands of the altered metabolism of fasting. For this reason, when a fasting animal is subjected to ether anesthesia the subsequent glycosuria is of a much less pronounced intensity than that following similar anesthesia in a well-nourished animal. The main factor in permitting the animal to replenish its depleted store of glycogen, i. e., the ingested food, is not present in the case of the fasting animal; therefore the glycogen lost through anesthesia stimulation is to a large extent a loss which cannot be made good. Thus the store of available glycogen is progressively decreased, a view which is in perfect harmony with the observation that the glycosuria becomes progressively less intense in the course of successive anesthetizations. Finally, after prolonged fasting only the reserve glycogen remains, and this glycogen, being uninfluenced by ether anesthesia even when induced for long periods, fails to lend itself to the production of postanesthetic glycosuria. In the case of the animals here reported on, the store of available glycogen was apparently depleted at the end of twenty-six to twenty-seven days. Dyspnea, as previously discussed, may have been a contributing factor in the production of the glycosuria observed.

SUMMARY

The investigation embraced a study of the glycosuria following ether anesthesia. Experiments were made on well-nourished and fasting dogs. Eleven tests were made on the well-nourished animals, the lengths of the anesthesia periods ranging from half an hour to four and one-half hours. Eight tests were made on dogs in different stages of fasting, the periods of anesthesia varying in length from an hour to six and three-quarter hours.

In the case of the well-fed animals the percentage of dextrose in the urine fraction first voided after anesthesia ranged from 1.32 per cent. to 6.94 per cent. In the case of the fasting dogs the percentage ranged from 0.52 per cent. to a negative test.

In a series of anesthesias induced on the same animal it was found that the fasting organisms showed a glycosuria of decreasing intensity. In one series, for example, the dextrose data obtained from four tests

were 0.43 per cent., 0.25 per cent., a trace, and a negative test. The well-nourished dogs did not show this uniformity.

In some of the experiments, made in series, on well-fed dogs there was a gradual decrease in the length of the period elapsing between the close of anesthesia and the voiding of the first fraction of urine. For example, with one animal, five tests showed the following decreasing latent periods: nine hours, six and one-half hours, six hours, four and one-half hours, two hours. This regular lessening of the latent period was not observed with fasting dogs. On the other hand, in certain cases, there was a progressive lengthening of the latent period.

In none of the experiments was there any regular relation between the specific gravity of the urine and its sugar concentration. Some of the urines of high specific gravity contained little or no sugar.

The glycosuria following the administration of ether to normal dogs persisted for from nine to twenty-seven hours, there being no regular relation between the length of the period of narcosis and the intensity of the subsequent glycosuria. The glycosuria noted in the fasting tests persisted from eleven to twenty-one hours.

After fasting from eight to eighteen days the animals exhibited a postanesthetic glycosuria only from one-thirteenth to one-fifth as intense as did normal dogs subjected to the anesthetic for similar periods.

That different organisms will react differently under the influence of similar anesthesia periods was clearly shown among other things by the wide variations in the intensity of the glycosuria produced. This was emphasized by the variation of the urinary sugar concentration from 2.73 per cent. to 6.94 per cent. in the initial fractions of urine following one hour's anesthesia in five different instances.

The above data are interpreted as indicating that the postanesthetic glycosuria observed was due primarily to the effect of the ether in stimulating the transformation of glycogen into dextrose. This deduction is further strengthened from the fact that in the experiments in which fasting animals were subjected to the influence of the anesthetic there was a much less pronounced glycosuria in the early days of the fast than had been previously observed in the case of the normally nourished animals, and further that when the fasting period was sufficiently prolonged (twenty-six to twenty-seven days) there were no signs of glycosuria even when the animals were subjected to long periods of ether narcosis.

A certain proportion of the glycogen of the animal organism may be considered as a reserve to be drawn on only in cases of great emergency, e. g., prolonged fasting. Ether anesthesia does not afford sufficient stimulation to cause the transformation of any part of this reserve glycogen into dextrose. The glycosuria in the case of well-nourished animals

results from the transformation of a portion of the glycogen in excess of the reserve. In the fasting organism this excess glycogen is gradually reduced in amount and finally completely exhausted through the altered metabolism of fasting. This, I take it, is the explanation for the slight glycosuria observed during the early days of the fast, a glycosuria which gradually decreases in intensity as the fast progresses and finally ceases to appear when the fast is sufficiently prolonged.

Dyspnea may also have been a contributing factor in the production of the glycosuria.

POSTANESTHETIC GLYCOSURIA OF SURGICAL PATIENTS

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At the time that Dr. Hawk was conducting his experiments on the effects of ether anesthesia on the metabolism of dogs, I was pathologist to St. Mary's Hospital, of Philadelphia. I was interested in the fact that many of the dogs subjected to prolonged anesthesia had glucose in their urines for varying periods after the administration of the ether. I undertook at that time to see whether ether as administered in the course of the regular surgical service of a hospital was in any case followed by the excretion of glucose. The plan was to record the time of the beginning of the administration of the anesthetic, the time that the administration was discontinued, the quantity of ether used, and whether there were any complications of anesthesia during the administration of the ether. Then the urine was to be collected as it was passed for at least two days after the anesthetization and each specimen examined for the presence of glucose. The study was begun, and was conducted on sixteen patients, but the work was interfered with and had to be discontinued. The facts are here given for what they may be worth in the future to some investigator who may wish to take up the subject again.

Of the sixteen patients examined, ten had no glucose in the urine either before or after the administration of ether for anesthesia for the performance of surgical operations as recorded by the Fehling test. One patient had no glucose before the administration of the anesthetic, but showed glucose in the urine once after the administration of the ether, although this patient was said to have had glucose in her urine once one month before she was operated on. One patient was operated on in an emergency and his urine was not examined before the surgical manipulation was begun; he had no glucose in his urine after the operation. Two patients had glucose in their urines both before and after the administration of the ether. Two other patients had no glucose in their urines before the operation; but showed glucose in their urines after the operation in considerable quantity. In one of the latter cases the excretion of glucose amounted to 39.0334 gm. during the nine days that the patient (aged over 60) lived after the operation for the removal of an epithelioma of both lips, the anesthesia lasting one hour and ten minutes, and 300 c.c. ether having been used. This patient died; but no autopsy was obtained. In the other case a man aged 80 years was operated on for the amputation

of a leg for senile gangrene. The etherization required thirty-five minutes, and 105 c.c. ether were used.

Of the two patients in whose urines glucose was present both before and after the etherization, one was a woman aged 46 who was operated on for the repair of a laceration of the pelvic floor; the other was a woman aged 25 years, who was operated on for the relief of a movable kidney. In the former the etherization lasted one hour and twenty minutes; in the latter one hour and ten minutes. In the first case 427.5 c.c. of ether were used and 300 c.c. were used in the second case.

During the progress of the examinations I noticed that many of the specimens became almost black after being allowed to stand in the laboratory for a few days, in spite of the addition of thymol for preservation. Some of these specimens contained a substance that reduced Fehling's solution and gave a positive reaction for glucose with Boetger's reagent and with the Brücke lead process, but failed to ferment or to give typical crystals of phenylglucosazone with phenylhydrazin hydrochlorid; two of these have been included in the above cases said to present glucose in the urines after operation. It was thought that this substance, which became black on standing, was homogentisic acid; but treatment of a fresh specimen with a 10 per cent. solution of sodium hydroxid failed to produce blackening. The identity of the body producing this change in color was not determined.

MALIGNANT TUMORS OF THE ADRENAL*

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Malignant tumors, primary in the adrenal glands, are of interest to the surgeon and to the pathologist alike. To the surgeon the chief interest centers in the problems of clinical diagnosis and treatment; for the pathologist the comparative rarity of such growths, certain features of their clinical symptoms, and the possible relation of such tumors to malignant hypernephromas of the kidney, combine to make this field one for constant observation and research.

Williams[1] out of a series of 8,378 consecutive cases of malignant tumors in some part of the body, found only one which was primary in the adrenals; Matter[2] found one case in a series of 3,100 autopsies; Hodge,[4] eleven in 6,200 autopsies; Gwilt,[5] none in 13,971 autopsies, while Brüchanow,[6] at Prague, found in the autopsy records of the Pathological Institute for the years 1884 to 1899, inclusive, but thirty-three primary adrenal tumors, only eight of which were malignant.

The symptoms produced by such tumors which are of especial interest to pathologists are those which seem to give some indication of the function of the gland itself, and are associated principally with the occurrence of the tumor in children. They are gigantism and a precocious development of the sexual characteristics. We thus have records of infants two or three years of age possessed of extensive growths of pubic hair, well-developed mammary glands, and hypertrophic external genitalia. The expectation that evidences of an increased secretion of epinephrin would be forthcoming in patients with adrenal tumors has not been fulfilled, while analyses of such tumors with a view to the demonstration of epinephrin have, apparently, not been made. In only one instance, to my knowledge, has this been done: thus, Davidsohn, in discussing Winkler's paper[7] on hypernephromas, mentioned a melanoma of the adrenal which he had recently studied. Extracts from the metastases in the great

* From the Pathological Laboratories of the University of Chicago.

1. Williams: Lancet, London, 1897, i, 1261.
2. Matter: Quoted by Lasagna, Virchow's Arch. f. path. Anat., 1910, cci, 282.
3. Lasagna: Zur Kenntnis bösartiger Nebennierengeschwülste, Virchow'sArch. f. path. Anat., 1910, cci, 282.
4. Hodge: Quoted by Lasagna: (Note 3.)
5. Gwilt: Quoted by Lasagna (Note 3).
6. Brüchanow: Ztschr. f. Heilk., 1899, xx, 39.
7. Winkler: Jahresb. d. Schles. Gesellsch. f. Vaterländ. Cult., 1908, lxxxvi, 189, Med. Section.

omentum yielded positive color, frog's-eye and blood-pressure tests for epinephrin. Bronzing of the skin, as in Addison's disease, is rare, though in about one-third of the cases, according to Ramsey,[8] a certain darkening of the skin has been described.

Regarding the relation of primary tumors of the adrenal to hypernephromas, the most diverse opinions are expressed. Stoerk[9] maintains that hypernephromas and adrenal tumors are fundamentally different, and that hypernephromas of the kidneys or other organs bear no relation to adrenal tissue, discrediting entirely the Grawitz theory of their origin. Stoerk's argument is as follows:

> The so-called hypernephromas are all fundamentally of a structure tending to the production of spaces and intracystic formations, such as could only arise from a tubular matrix—in this instance, the kidney. Tumors arising from solid organs such as the adrenals should in turn be solid. Therefore it is clear why true adrenal tumors, which are much more rare than "hypernephromas of the kidney," differ distinctly from the latter. In both types of tumor there is a certain arrangement of the cells into columns and groups. This same structure is to be found, however, in tumors of undoubted renal origin. Adrenal cells and hypernephroma cells differ entirely from each other; the latter resemble very closely certain cells which are found in the large white kidney and in the secondarily contracted kidneys.

Exception was immediately taken to Stoerk's argument, it being maintained that the statement that tubules never were found in the adrenal was incorrect since such structures had been described by Askanazy,[10] Marchand,[11] and others. Gatti[12] denies any essential difference in the appearance of hypernephroma cells and adrenal cells and champions the view of the adrenal origin of hypernephromas. This is the conclusion apparently arrived at by Garceau[13] when he intimates that hypernephromas and malignant tumors of the adrenal are practically identical. Accordingly, to Garceau the chief characteristics of a malignant growth of the adrenal are the following:

> "The tumor is either single or multiple; when multiple the growth is composed of variously sized nodules, each surrounded by a capsule, which limits it from the surrounding adrenal tissue. The large tumors may reach a good size, even that of one or two fists or much larger. Metastasis is mainly through the circulatory system; the organs chiefly attacked are the lungs, liver, and bones. It is to be remarked that the organs attacked secondarily are those chiefly attacked by hypernephroma of the kidney. The metastases resemble the parent tumor and bear a striking resemblance to a hypernephroma of the kidney. These peculiarities are strong proof that the Grawitz tumor in the renal parenchyma is derived from adrenal 'rests' in the kidney.

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8. Ramsey: Bull. Johns Hopkins Hosp., 1899, x, 20.
9. Stoerk: Beitr. z. path. Anat. u. z. allg. Path. (Zeigler's), 1908, xliii, 393.
10. Askanazy: Berl. klin. Wchnschr., 1908, xlv, 1603.
11. Marchant: Quoted by Zehbe, Virchow's Arch. f. path. Anat., 1910, cci, 150.
12. Gatti: Virchow's Arch. f. path. Anat., 1896, cxliv, 467.
13. Garceau: Tumors of the Kidney, 1909, p. 278.

"Under the microscope malignant tumors of the adrenal resemble markedly the cortex of the normal adrenal body, both in the form and arrangement of the cells. In some places the arrangement suggests that of the zona reticularis, in others that of the zona fasciculata. Thin-walled capillaries surround the groups of cells, which are arranged in columns or rows two or three cells deep in alveolar form, and connective tissue septa from the capsule of the tumor penetrate the growth and divide it into separate parts. The cells, in rows, are placed directly on the capillary vessels, as in hypernephromas of the kidney; the first row is placed tolerably perpendicularly on the walls, and the others rather irregularly; they have large nuclei, are polygonal in shape and contain vacuoles which correspond to areas which formerly contained fat which has been extricated in the process of mounting. The shape of the capillary interspaces between the tumor cells is often quite irregular. Evidences of hemorrhage and necrosis are seen in places."

Additional data bearing on this subject have been furnished from the fields of comparative pathology and chemistry. From the former[14] has come evidence that hypernephromas of the adrenal cortex of cattle agree in their macroscopic and microscopic structure, in their retrogressive changes and in their glycogen and lecithin content with the Grawitz kidney and adrenal tumors of man. This fact, taken in conjunction with the observation that while adrenal rests and hypernephromas are common in the kidney but rare in the adrenal in man, and that the reverse is true in cattle, may easily be interpreted in favor of the Grawitz theory. Chemical studies by Wells[15] and others had indicated that the lecithin and cholesterin content of renal hypernephromas agreed very closely with that of normal suprarenal tissue, while that of other tumors did not, and it was suggested that the determination of the lecithin content of a tumor would afford a reliable means of determining its adrenal origin. Steinke[14] in a recent study could not confirm these results as applied to bovine hypernephromas, but considers that with human hypernephromas the chemical characteristics deserve consideration in differential diagnosis. It has also been stated that extracts of hypernephromas resemble adrenal extracts and differ from the extract of other tumors in their ability to decolorize iodized starch solutions,[16] but the specificity of this reaction has been questioned.[17] Fölger[18] is said to have demonstrated epinephrin in hypernephromas of animals by the blood-pressure method, while Steinke[14] claims to have isolated the substance by chemical methods. In identifying the substance isolated, however, Steinke used purely chemical, not biological tests, so that his results are not so satisfactory as might be desired. Fölger's "hypernephromas" were primary in the adrenal of

14. Steinke: Frankfurt. Ztschr. f. Path., 1910, v, 167.
15. Wells: Internat. Clin., series 18, 1908, ii, 273; Jour. Med. Research, 1908, xvii, 461.
16. Croftan: Virchow's Arch. f. path. Anat., 1902, clxix, 352.
17. Körber: Virchow's Arch. f. path. Anat., 1908, excii, 356.
18. Fölger: Monatsh. f. prakt. Tierheilk., 1908, xx, 145.

horses and, as Greer and Wells[19] suggest, it is not certain that normal adrenal tissue may not have been included in the mass from which he made the extract. It is interesting to note that most observers have failed to demonstrate epinephrin in hypernephromas of man, the reason assigned being that while epinephrin is produced by the medullary cells of the gland, hypernephromas arise from the cells of the cortex.[19]

Recently Zehbe[20] has presented strong histological evidence in support of Stoerk's view. He has been able to trace the development of typical hypernephroma cells from cells of the renal tubules, from connective tissue cells, and from endothelial cells. He concludes an exhaustive comparative study of a long series of normal embryonic and adult adrenals, nephritic kidneys and tumors of the adrenals and kidneys as follows:

A complete summary of all the facts brought out in this work shows that the epithelial tumors in the kidney are all of one origin; that is, the renal epithelium. The line of proofs for this statement may be considered as being of both a negative and a positive character. On the negative side we have the observation that the alleged characteristics of "hypernephromas" are to be found in the kidneys and in lesions developing in and from them, as well as in the adrenal and its tumors; for example, cells whose protoplasm has a foamy structure due to the infiltration of fat, giant-cells and a definite supporting capillary network.

On the positive side we find peculiarities in the structure of hypernephromas which find their explanation and analogy not in the adrenal, but exclusively in the kidney. In this category belong the observations that the kidneys may give rise to tumors of a solid or of a tubular structure, while in the adrenals only the former type occurs; moreover in these tumors fat-free cells occur such as are never found in the adrenal, but are common in the kidney; also hydropic, so-called "glassy" cells are found in the kidney, but never in the adrenal, the cells of which are of a "foamy" structure with well-stained protoplasm. In addition we have the citation of two typical hypernephromas developing in the pelvis of the kidney, and of the fact of the relationship between contracted kidneys, regenerative processes and tumor formation in the parenchyma of such kidneys. Zehbe does not deny that adrenal rests may give rise to tumors; in fact, he is inclined to believe that Neuhäuser[21] has described such a lesion. He does not consider it necessary to regard hypernephromas arising in the region of the sexual organs, the liver, the pancreas, or in any place where aberrant adrenal tissue may be found, as being necessarily of adrenal origin, since he has demonstrated that "hypernephroid" cells may arise from connective tissue or endothelium. On

19. Greer and Wells: THE ARCHIVES INT. MED., 1909, iv, 291.
20. Zehbe: Virchow's Arch. f. path. Anat., 1910, cci, 150.
21. Neuhäuser: Quoted by Zehbe (Note 20).

such a basis he considers that the tumors in joints diagnosed as endotheliomas by Driessen,[22] Hildebrand,[23] and Paoli,[24] but as metastatic hypernephromas by supporters of the Grawitz theory, were probably of the former type, in which the cells had developed "hypernephroid" characteristics. Likewise he reminds us that the lutein cells of the ovary and the interstitial cells of the testicles are of this hypernephroid structure and that these cells may give rise to tumors.

The adrenals themselves and adrenal tumors, according to Zehbe, are always of a solid structure, never tubular; the smaller tumors present a distorted though very marked resemblance to adrenal tissue, while in the malignant tumors this similarity is much less noticeable. The tumor-cells show a tendency to depart from the adrenal type; the sharp outlines of individual cells becomes less distinct; the division of the cell mass into slender columns is more or less lost, and may be entirely absent in malignant tumors. Fat and doubly refractive substances occur in large though inconstant amounts. It is their presence which accounts for the "foamy" or "honeycomb" structure of the cell protoplasm. The cells are mostly round or polygonal in shape, seldom elongated. Giant cells are found in malignant tumors. Hydropic (glassy) cells do not occur.

The evidence thus far advanced on both sides of this question has its strong points, and one cannot but feel that a positive decision based on the one or the other line of argument would be unwarranted. There is, however, another point of view from which the problem may be attacked. Adami,[25] on an embryological basis, considers that typical hy[illegible]romas may arise from either renal or adrenal tissue. His statement is as follows:

> We are of the opinion that this latter view must be accepted, that whereas aberrant adrenal tissue is, from its heterotropic nature, more prone to become blastomatous, and whereas, it may well be that a large number of the kidney tumors of this type are hypernephromas, others are "nephromas." We certainly encounter typical tubular or cystic adenomas of renal origin, and know now that what we once regarded as the conclusive demonstration of adrenal nature, namely, the presence of glycogen (Lubarsch), is of little diagnostic value. A very large number of embryonic tissues, as again of freely growing tumors, contain glycogen in their cells. When a tumor of the kidney shows a special liability to form tubules rather than solid cell masses, one would suspect a renal rather than an adrenal origin. Not to enter exhaustively into the subject, we would say that the two organs are embryogenetically so closely related that tumors arising from homologous tissues must possess closely related characters. When, as is most frequent, but by no means constant, one of these growths arises from the upper pole of the kidney, there the probabilities are that it is of adrenal origin. ....If a convenient term is required for all this order of tumors, the transitional

22. Driessen: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1893, xii, 65.
23. Hildebrand: Arch. f. klin. Chir., 1894, xlvii, 225.
24. De Paoli: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1890, viii, 140.
25. Adami: General Pathology, 1908, pp. 795 and 650.

adenocarcinomas of adrenal, kidney, ovary and testis, we have, from embryogenetic consideration, suggested the term, mesothelioma.

Briefly, a mesothelioma is: (1) A tumor arising from such tissues or portions of organs as, being of mesothelial origin, possess in the adult state lepidic characters. (2) When typical and growing slowly, it is of pure adenomatous type. (3) When atypical or more anaplastic, and growing rapidly, it reverts first to an alveolar sarcomatous type, and later to a structure, or want of structure, which renders it indistinguishable from a round or a short spindle-celled sarcoma. (4) The tumor, when it takes on this undifferentiated type, affords metastases of a sarcomatous order. The primary growth in general, if studied, exhibits indications of the successive stages through which it has passed, from the adenomatous to the sarcomatous form of growth. .. (p. 745).

And what appears to be an adequate reason for this difference in properties suggests itself. As we have emphasized more than once, properties which are of oldest acquirement are those which are last to be lost; those of later acquirement are yielded up with greater ease. The primary lepidic tumors are derived in direct descent from cells which, from being lepidic (in hypoblast or epiblast), have become hylic, and only at a later embryonic period have taken on lepidic characters. Such cells in new growths revert more easily to the hylic, sarcomatous type, than do the cells of the primary lepidic tumors (p. 650).

And now the question arises, does this very interesting hypothesis exactly fit the facts in the case? Does it explain the contention of Stoerk, confirmed by Zehbe, that whereas primary malignant tumors of the adrenal are essentially "solid" in structure, hypernephromas abound in tubulocystic areas? Does it explain the rarity of hypernephromas of the kidney on the one hand and, on the other, the relative abundance of primary malignant tumors of the adrenal in children? Does it explain the presence of hydropic or "glassy" cells in hypernephromas and their absence in adrenal tumors? Does it account for the absence of symptoms referable to the adrenal in hypernephromas of children and the presence of such symptoms in children with malignant adrenal tumors? May not the histogenesis of the kidney and adrenal warrant a somewhat different interpretation? As the answer to this last query must form the basis for our discussion, let us consider it first.

It is generally admitted that the origin of the medullary portion of the adrenal glands is in the sympathetic nervous system. As to the origin of the cortical portion of the gland, opinion is divided, though recent work[26] on the subject indicates that it arises from the celomic epithelium. The process of differentiation in the chick as described by Lillie[27] is as follows:

According to Soulié the cortical cords arise as proliferations of a special suprarenal zone of the peritoneum adjacent to the anterior and dorsal part of the germinal epithelium. This zone is distinguishable early on the fourth day, and begins about half a millimeter behind the glomeruli of the pronephron, extending about a millimeter in a caudal direction. Proliferations of the peritoneal epithelium are found in this zone, and soon becomes detached as groups of epithelial

26. Poll: In Hertwig's Handbuch der vergleichenden und experimentellen Entwickelungslehre der Wirbeltiere, 1906, iii, part 1, p. 443.

27. Lillie: Development of the Chick, 1908, p. 404.

cells lying in the mesenchyme between the anterior end of the Wolffian body and the aorta. Such proliferation continues up to about the one-hundredth hour or a little later, and a second stage in the development of the cortical cords begins; the cords grow rapidly and fill the space on the mediodorsal aspect of the Wolffian body, and then come secondarily into relation with the renal corpuscles of the latter and the sexual cords.

According to Semon and Hoffmann the relation thus established is a primary one; that is to say, the cortical cords arise from the same outgrowths of the capsules of the renal corpuscles that furnish the sexual cords. Rabl agrees essentially with Soulié, and it seems probable that Semon and Hoffmann have overlooked the first stages in the origin of the cortical cords of the suprarenal capsules.....The organ has become vascular, and the vessels have the form of sinusoids, i. e., they are molded on the surface of the cords with no intervening mesenchyme.

As is well known, the kidney arises in two divisions, so to speak. The ureter, pelvis and the collecting tubules appear as an outgrowth from the Wolffian duct; the capsule of Bowman and the collecting tubules are formed in and from the solid mesenchyme.

From the above descriptions it is to be seen that the adrenal cortex and the kidney, though both of mesodermal origin and hence secondarily hylic, arise from different types of cells. It may be objected that no sharp distinction can justly be drawn between the mesothelium and the mesenchyme, since the mesothelium is merely such part of the mesenchyme as bounds the body cavities. It would seem, however, that the very fact that the one gives rise to the lining of the peritoneal cavity and the adrenal cortex, for instance, while from the other such structures as the kidneys and the connective tissue of the peritoneum are produced, in itself is sufficient evidence of a difference and a distinction. It is here that Adami's generalization fails to satisfy all the conditions, for while tumors of adrenal origin, depending on their degree of malignity, would present all varieties of structure from the normal down through alveolar carcinomas or sarcomas, to typical endotheliomas, or even round-cell sarcoma, tumors of renal origin would graduate from the simple tubular or possibly papillary type, through the various grades of the adenosarcoma with variously distorted tubular structures, to the pure sarcoma. This agrees well with the contention of Stoerk and Zehbe that tumors of adrenal origin are solid, in contrast to those of renal origin and, with the knowledge that renal epithelial cells are prone to exhibit hypernephroid characteristics, would seem to furnish further evidence of the independence of the adrenals and malignant hypernephromas, and of the renal origin of the latter.

Accepting the view that hypernephromas and malignant tumors of adrenal origin are different entities, we are rid of the necessity, in so far as the present discussion is concerned, of attempting to explain the rarity of hypernephromas, and the relative abundance of malignant tumors of

the adrenal in children, while we find a ready explanation for the lack of specific symptoms in the former, and their presence in the latter cases.[28]

Before one can finally agree with Stoerk, however, the observations of Steinke regarding hypernephromas in the adrenal glands of horses and cattle must be explained. With this exception the evidence seems to point strongly toward the renal origin of hypernephromas.[29]

In this connection the report of an instance of a primary malignant tumor of the adrenal may be of interest.

REPORT OF CASE

History.—A. F., a Syrian, aged 25, entered Cook County Hospital Oct. 6, 1909, with a clinical diagnosis of tuberculosis of knee and hip-joint, and miliary tuberculosis. Five years ago the patient was kicked by a mule on the right hip. For two months before admission to the hospital he had pain about the back and right hip. The pain gradualy grew worse and for twenty days previous to admission to the hospital the patient had not been able to work.

Examination.—At the time of admission the spleen was enlarged and palpable and a tumor could be palpated just below the tenth rib. A mass of enlarged lymph-glands was visible in the left supraclavicular region. There was general adenopathy. The right leg was much swollen and the tissues over the head of the femur were swollen and tender; the left leg was normal. There was no tenderness along spine. Temperature and respirations were normal on admission; pulse high; leukocyte count, 10,000. The temperature remained normal for the most part; pulse always a little high. After a time there was some urinary retention. The patient died Nov. 23, 1909, and the post-mortem examination was made by Dr. H. Gideon Wells, Nov. 27, 1909.

Anatomical Diagnosis.—Primary malignant neoplasm of right adrenal, with massive metastases in regional lymph-glands; secondary growth in left cervical, mediastinal, mesenteric, retroperitoneal and iliac lymph-glands; metastases in lungs, pleura, dura mater, skull, liver, right kidney, left adrenal, eighth rib, pubic bone and upper portion of right femur, with pathologic fracture of femur; injection of lymphatics of surface of lung, with tumor cells; thrombosis of right external iliac and femoral veins, with edema of right lower extremity; dilatation

28. Garceau (see note 13) found but four hypernephromas in children out of a series of 176 cases, while Franck (Beitr. z. klin. Chir., 1910, lxvi, 11) claims that there are only four cases on record; of sixty-seven cases of tumors of the adrenal, on the other hand, Ramsey (see note 8) found that six were in children and eight were registered as being in patients "under 20"; and Garceau collected reports of twenty-five cases in children.

29. Since the above was written, Wilson and Willis (Jour. Med. Research, 1911, xxiv, 73) have reported the results of their study of fifty-four renal tumors, forty-eight of which were so-called hypernephromata; twenty-six swine embryos (serial sections), 5 to 20 mm.; forty-three human embryos (serial section), 6 to 70 mm. They conclude that most, if not all, so-called adrenal rests are probably of Wolffian origin. There is almost no evidence, embryologic or histologic, in support of Grawitz' hypothesis that the so-called hypernephromata have their origin in adrenal rests. There is much evidence that the so-called hypernephromata do not arise from proliferations of the adult secreting epithelium of the convoluted tubules. There is much evidence that the so-called hypernephromata do arise from islands of nephrogenic tissue. Such tissue is sometimes present in the adult kidney and appears capable of forming tumors of the non-infiltrating mixed cordon, tubular, papilliform, and sarcoma type so characteristic of the so-called hypernephromata.

of urinary bladder and ureters, with slight hydronephrosis, and concretions in pelvis of kidneys; acute parenchymatous nephritis; hypostatic edema of lung; passive congestion of spleen with fibrous perisplenitis; multiple *Tænia saginata;* operative incision in right leg; diffuse arteriosclerosis; tumor thrombosis in right renal vein.

External Appearance.—The body is that of a poorly nourished, swarthy man. There is a marked difference in the appearance and position of the lower extremities. The right leg lies in a characteristic, everted position and is greatly swollen throughout, the swelling being rather hard. The body shows considerable postmortem decomposition; no icterus; tattooing on arms and hands. In the left supraclavicular region is a large mass of glands. A marked grating sensation is felt on rotating the right leg; rotation is very easy, the joint being extremely loose; large play of movement; the right leg moves more freely than the left. Over the upper end of the tibia on the right aspect is a discolored scar; over the middle of the posterior aspect of leg is another round pigmented scar; bed-sore over sacrum. In the middle of the thigh on the posterior aspect is an incision apparently rather recent. The skin here is somewhat undermined but no distinct fistulous tract can be found; markedly edematous condition of skin on cutting into leg at this point; the incision does not extend deeply; muscles and other tissues are much water-logged; over the vicinity of the greater trochanter and the neck of the femur is a mass of disorganized tissue containing spicules of bone. On cutting into this tissue a chocolate-colored, purulent fluid containing fragments of bone is discharged. The upper end of the femur has suffered solution of continuity just below the greater trochanter site of pathological fracture; periosteum much thickened and yellow; a great deal of newly formed white tissue is present over the surface of the trochanter, and in places there are distinct masses of whitish, rather firm tissue occurring in nodules, in which yellowish areas can be seen. On dissecting out the upper end of the femur the periosteum is found to be nearly 1 cm. thick. The periosteal thickening continues downward for some distance, but the periosteum is detached from the femur for about 7 cm. Below this point the periosteum is attached to the bone and gradually becomes of normal thickness. In close relation to the middle of the femur are a number of branches of the femoral vein which are thrombosed, with rather recent, firm, ante-mortem clots. Where the periosteum has separated from the femur, the bone is rough and eroded. Necrosis and liquefaction seems to extend more on the anterior than on the posterior surface; the large vessels of the leg are entirely occluded by thrombi and all ramifications of deep vessels are occluded by firm thrombi; the hip-joint is absolutely uninvolved. After removing the head of the femur, there is found on the medial aspect of the thigh a firm swelling in the vicinity of Poupart's ligament, and above Poupart's ligament, a large gland; a few slightly enlarged glands on the left side above Poupart's ligament; axillary lymph-glands only slightly enlarged.

Abdominal Cavity.—On opening the abdomen a small amount of fluid is found; external surface of greatly distended urinary bladder is studded with white nodules; urinary bladder reaches to within two fingers' breadth of umbilicus; posterior surface of bladder also studded with white nodules. Appendix is free; inguinal and femoral rings are closed; mesenteric lymph-glands are all more or less enlarged; enlarged bladder fills pelvis; pelvic glands are enlarged; entire retroperitoneal region is filled with a solid mass of tissue. The liver is adherent throughout entire anterior surface to diaphragm; gall-bladder somewhat distended; spleen greatly enlarged and imbedded in adhesions; lower end of spleen comes exactly to costal margin; gall-bladder imbedded in adhesions, and in these adhesions are whitish nodules up to 1 cm. in diameter. Many of the mesenteric lymph-glands are 1 to 2 cm. in length and thickness, some being white, some dark.

Pleural Cavity.—Sternum and tissues of anterior mediastinum show no gross abnormalities; lungs meet in median line, retract poorly and have many fibrous

adhesions; adhesions very firm about apex of lung and about diaphragm on left side; surface of the pleura is smooth and shiny. On the superior surface of the diaphragm are a number of whitish nodules, some 1 cm. in diameter. In the thoracic cavity along the vertebral tissue is a chain of enlarged lymph glands.

Pericardial Cavity.—This contains considerable blood-stained fluid; surfaces of the pericardium are smooth and shiny.

Upper Alimentary and Respiratory Tracts.—The tongue and pharynx, esophagus, larynx and trachea show no abnormalities. At the bifurcation of the trachea are large anthracotic lymph-glands in which whitish nodules stand out.

Heart, Aorta and Great Vessels.—Heart of about normal proportions; coronary vessels very tortuous, decidedly thick-walled; muscle of heart firm; beginning of aorta shows a few atheromatous patches; coronary vessels where cut across stand out and are distinctly thickened. Thickening of coronary arteries is diffuse; no marked patches; aortic, pulmonic, mitral and tricuspid valves normal; foramen ovale closed; muscle hard, rather light in color; weight of empty heart, 300 gm.

Lungs.—The lungs do not collapse very well; pleura shows network of irregular white lines, rough to touch, with occasional pea-sized, whitish nodules. In the left lung this is most marked on the anterior surface of the upper lobe. Nodules can be palpated in the substance of the lung beneath the injected lymphatics. The lungs feel boggy; full of liquid. In places throughout the lungs nodules can be palpated. The same peculiar lymphatic distribution of tumor cells persists throughout the lung itself; the lower lobe contains a great deal of fluid, and occasionally a pea-sized whitish nodule. The right lung also is heavy with fluid. Its surface shows a similar network of injected lymphatics, and tumor nodules can also be found; no large tumor nodules in either lung; the largest the size of a pea.

Liver.—This organ is adherent anteriorly to diaphragm, posteriorly the right lobe is adherent to peritoneum over a great tumor mass on the right side; surface of liver shows an occasional whitish nodule, 1 to 4 mm. in diameter; no stones in the gall-bladder. Within the liver substance are occasional whitish nodules, none more than pin-head size, and most abundant near capsule. There are perhaps fifteen to twenty nodules in all, mostly on the posterior surface of the liver. The liver itself is rather pale, but otherwise shows no changes. The weight of the liver is 1,800 gm.

Spleen.—The weight of spleen is 1,000 gm.; the spleen does not seem to be involved by the tumor growth, but is firmly adherent to the diaphragm and surrounding viscera, and is imbedded in a mass of adhesions. The spleen is greatly enlarged. It is doubled on itself but is nowhere infiltrated by the tumor. It is of normal consistence and contains a great deal of blood. The Malpighian bodies are rather prominent. The splenic artery is much enlarged and its walls are thick and tortuous.

Pancreas.—The pancreas itself, although lying close to the tumor mass, shows no changes. The lymph-glands in its vicinity are large and white. There are tumor nodules in the root of the mesentery.

Gastro-Intestinal Tract.—The stomach shows no abnormalities. In the intestines are found a number of tapeworms, probably the beef tapeworm, *Tænia saginata*.

Tumor in Situ.—The whole retroperitoneal region is filled with a huge tumor mass which lies pretty symmetrically, with its long axis extending from the level of the left sacro-iliac junction, upward to the right. The mass is lobulated and not hard, apparently consisting chiefly of greatly enlarged retroperitoneal lymph-glands. In some places it is rather soft, in other places about the consistency of normal kidney. The lower part lies to the left of the median line, the upper part to the right. There has been a great distortion of tissues, the abdominal aorta and the inferior vena cava being two inches apart. The largest part of the tumor is a globular mass measuring 16 by 13 by 10 cm. It lies in the right

retroperitoneal region and pushes upward the liver, to which it is adherent. The large mass is round and smooth, and probably is the primary growth. The lower border lies at the level of the twelfth rib in the mammary line, the upper border at the upper margin of the fourth rib, and posteriorly the upper margin is at the level of the attachment of the eighth rib to the vertebral column. Running along near Poupart's ligament are large dark-colored lymph-glands containing white nodules. The femoral vein is occluded by a huge, dry, ante-mortem tumor-thrombus, the thrombus extending in the external iliacs up to the junction with the internal iliacs. The lymph-glands along the femoral and iliac veins are enlarged. The cul-de-sac of Douglas contains many tumor-nodules in the peritoneum. A tumor mass involves the right pubic bone and extends over the median line to the right. The tumor extends up along the ramus and along the margin of the pelvis but does not infiltrate the acetabular cavity. The pubic bone is almost entirely replaced by tumor growth of a peculiar yellow color, with areas of necrosis. The posterior part of the pubic bone, the descending ramus, is also infiltrated.

Genito-Urinary System.—Both ureters are considerably distended, as is the urinary bladder. The testicles show no abnormalities. The prostate is not enlarged or involved by the tumor. The urinary bladder is greatly distended and on its external surface are many small nodules. None is present on the internal surface of the bladder. The left kidney is much enlarged. This enlargement is due in large part to dilatation of the pelvis, which contains a large quantity of yellow, granular, sand-like material. The cortex is distinctly thickened and rather reddish in color, measuring 1 cm. The pyramids are somewhat shortened from pressure. The kidney is red, soft and drips with blood. The kidney on this side is not attached to the surrounding tissues aside from the tumor mass in the median line. The right kidney is directly below the large tumor mass, which is distinctly yellow and is intimately related to the upper pole of the kidney. The kidney contains many yellowish nodules and one of the large renal veins contains a tumor thrombus. A large number of tumor nodules are scattered throughout the kidney, the largest 2.5 cm. in diameter. The kidney itself proves not to be continuous with the large tumor mass which lies above it, but is separated by the capsule. The kidney tissue between the tumor nodules resembles that of the opposite kidney.

Adrenals.—No trace of the right adrenal can be found, its place being taken by the large globular tumor. The smaller nodules on the surface of the tumor are enlarged lymph-glands. The left adrenal is in its proper site and is not enlarged but is infiltrated with tumor nodules of pin-head size.

Lymph-Glands.—The large mass of glands in the left supra-clavicular region measures 12 by 9 by 4 cm. These glands contain yellowish tissue with a tendency towards diffuse necrosis and softening.

Brain and Meninges.—In removing the calvarium we find places on the internal and external aspects of the bone, but showing best on the internal aspect, where the bone is distinctly involved, and beneath which are yellowish thickenings in the dura. These are most distinctly seen in the left parietal region and are made up of the same whitish tissue seen elsewhere. The metastases in the dura are 3 to 5 mm. thick. The brain on its external surface shows no abnormalities. Weight of brain, 1320 gm.

Skeleton.—At the junction of the eighth rib with the vertebral column is a distinct tumor growth 2 cm. in diameter, infiltrating the head of the rib; head of eighth rib almost entirely destroyed; vertebræ do not seem to be involved; pathological fracture of right femur as described above.

Structure of Tumor.—Further examination of the main tumor after saturation with Kaiserling's solution discloses the following conditions: The mass is nearly square in outline, and measures 25 cm. in greatest breadth, 26 cm. in length, and 10 cm. in thickness. It consists of numerous, encapsulated, smooth,

rounded whitish nodules varying in diameter from a millimeter to the 16 cm. of the primary growth. At the upper right-hand corner is the egg-shaped primary growth occupying the site of the right adrenal. It is firmly attached to the upper pole of the right kidney, though distinctly separated from it by a definite capsule 1.5 mm. in thickness. On section this mass shows (1) the enclosing capsule, (2) just within the capsule a rim of tissue from 0.5 cm. to 2 cm. in width, whose inner margin is very irregular, and which presents a fairly homogeneous grayish white surface. This "rind" goes over with no sharp line of demarcation into, (3) the large central mass, which is made up of very irregular intersecting bands and strands of fibrous tissue, between which is a soft, very friable, yellowish-white matrix. This structure is frequently interrupted, especially near the center of the growth, by cavities, which, apparently, represent nothing more than areas of liquefaction necrosis. The cut surface of the other nodules presents essentially the same appearance, excepting that in the smaller ones the central necrosis with cavity formation is much less marked. In a few of the nodules, there are streaks of a peculiar yellowish-orange color which follow closely the connective tissue trabeculæ. They appear also to a limited extent in the primary growth, but not in the majority of the metastases. In one of the larger nodules is a diffusely outlined area 1.5 cm. in diameter of a dark reddish brown color, which probably signifies the presence of a hemorrhage.

Just beneath the primary growth, and, as mentioned above, firmly attached to it, is the right kidney. This organ is 12.5 cm. in length, the cortex measuring 10 to 15 mm., the medulla 20 mm. There are numerous whitish nodules scattered through it, mostly in the medulla; only the largest involves the cortex. The pelvis is entirely free from involvement except at two or three points where nodules in the renal papillæ have extended to the surface. The ureter worms its way among the tumor nodules, but nowhere has it been invaded in the least by the tumor tissues; it is patent throughout.

Turning now to the upper left-hand corner of the tumor mass, the left adrenal is found to occupy its usual position on the upper pole of the left kidney. The left adrenal is extensively invaded by tumor tissue. A strip of the organ 1.5 cm. in width and of about one-half the length lying on the medial surface of the upper pole of the kidney, is apparently all that remains of the normal gland, and even this contains a number of whitish nodules; lateralad and in direct continuity, is a nodule fully 2 cm. in diameter and 3 to 4 cm. in length of a gross structure quite similar to that of the other smaller nodules. The left kidney is entirely free from tumor growths; its cortex measures 10 to 15 mm., medulla, 20 mm.; it is 11.8 cm. in length. The pelvis is free, while the ureter, though like its mate on the right side, buried in the metastatic growths, is patent and entirely free from tumor infiltration. The left renal artery and vein, though much distorted by the tumor nodules among which they lie, are free from tumor tissue and are not thrombosed; the right renal artery is patent, and its intima is smooth, though it is firmly imbedded in the tumor mass. The right renal vein is partially occluded by a thrombus which extends along the entire length of the vein and projects into the vena cava, where it becomes continuous with a thrombus about 3 cm. in length, situated on the posterior segment of the wall of the latter vessel. These thrombi are firmly attached to the vessels. On attempting to dissect out the right renal vein and the vena cava it is found that as one approaches the point of origin of the thrombi the vessel wall appears to merge directly into the surrounding tumor, rendering a complete separation of vessel from tumor impossible.

Microscopic Examination.—For microscopical study tissues were fixed in Zenker's fluid; a few were fixed in 10 per cent. dilution of liquor formaldehydi, imbedded in celloidin and stained with hematoxylin and eosin and with Van Giesen's stain. Sections from the primary tumor appear as follows: At one border is the dense connective tissue capsule; just beneath this is a very richly cellular zone in which occasional islets of typical adrenal cortex—glomerulosa and

fasciculata—occur. These islets are immediately adjacent to the capsule, appear as though somewhat compressed, and pass over without a distinct line of demarcation into the mass of the tumor. They are not associated with the orange-yellow streaks mentioned in the gross description, and the more deeply lying cells have lost their nuclei and are distinctly necrotic. The tumor cells are densely packed together. Their nuclei are round or oval in outline, somewhat vesicular, with deeply staining chromatin granules and in many cases a well-marked, centrally placed nucleolus. They are larger and more deeply staining than the nuclei of the adrenal cells. Mitotic figures are occasionally found. The cytoplasm is fairly abundant, and only exceptionally can what appear to be small vacuoles be discerned in it. The cells, in general, are arranged in comparatively large, rather indistinctly demarcated groups in a wide-meshed network of narrow capillaries. In a few areas these "groups" appear in the form of broad, anastomosing bands, bounded by capillaries, in which case the cells bordering the capillaries are arranged fairly perpendicularly to the vessel wall. Intercellular connective tissue fibrils are found in some places but are absent in most. The capillaries in most places are not at all conspicuous, while in a few others they seem to form the core of columns of cells, the latter being arranged with their long axes at right angles to the thin vessel wall. In such cases the nuclei of the cells are situated in the portion of the cell which is farthest from the blood-vessel. This perivascular arrangement, though rare, is especially noticeable in some of the metastases in the regional lymph-glands. Proceeding inward from the capsule, this cellular zone gradually gives place to a structure which is characteristic of the great mass of the tissue and agrees very well with the gross description; that is, there occurs an increasingly coarse framework of anastomosing connective tissue trabeculæ enclosing cellular masses. Occasionally lumina appear in these masses and then the tissue assumes something of a cavernous structure. Such lumina are usually empty, and one cannot definitely overcome the suspicion that many of them are artefacts. Not rarely one is found which is lined with a single layer of cuboidal cells thus tending to allay the suspicion just mentioned. In some areas the connective tissue trabeculæ form the major portion of the tumor, the tumor cells being crowded into narrow, communicating clefts. The larger trabeculæ frequently show evidence of a marked hyaline transformation. Large necrotic areas and empty spaces become numerous as the center of the tumor is approached. Hemorrhagic areas, relatively few in number, are scattered irregularly throughout the section.

Coronal sections through the left adrenal appear as follows: At the medial margin, tissue apparently normal in all respects, is encountered. As one proceeds lateralad, endothelial-like cells are found in the capillaries, especially in those of the medulla; at first isolated cells or groups of three or four cells are found whose nuclei are three or four times the size of the ordinary endothelium, and whose cytoplasm is abundant, is finely granular, and takes a purplish-red stain with the hematoxylin and eosin; such cells increase rapidly in number and a zone is reached in which strands, columns and nests formed of them fill the sinusoidal spaces and divide the adrenal tissue into small islets, while still further lateralad, adrenal cells are entirely absent and the tissue passes over insensibly into cellular masses of a structure similar to that of the "rind" of the primary tumor.

The metastases in the regional lymph-glands and in distant organs are essentially of this large-celled type, but rarely does the cellular arrangement of the "rind" occur. Of the metastases, those in the lungs are the most interesting histologically, in the great predilection which they show for dissemination by way of the lymphatics. Practically all of the lymphatic vessels accompanying the larger blood-vessels and bronchi are distended with masses of large endothelial-like cells. Sometimes the distended lymphatic is lined by several layers of such cells, while an empty space is found in the center, but as a rule spaces within the lymphatics, not occupied by cells, are filled with pink, granular material and cellular detritis. Occasional leukocytes of various types also occur. Points at

which tumor cells have broken into the alveoli of the lungs, forming tumor masses of from half a dozen cells to nodules with a diameter equal to that of six or eight alveoli occur commonly, especially in the neighborhood of the larger bronchi. The endothelial lining of many of the tumor injected lymphatics appears to be intact. The tumor cells in the metastases are considerably larger than those in the "rind" of the primary tumor, and as one studies sections from various portions of the growths, a gradual transition from the one to the other seems to become evident.

Many of the blood-vessels throughout all of the sections from the primary tumor, and in many of the sections from the regional metastases, are plugged with masses of blue-staining granules which probably represent bacterial emboli. They do not appear to have produced any change in surrounding structures. Polymorphonuclear leukocytes are to be found in considerable numbers in nearly all sections, though there are no localized accumulations.

The frog's eye test, the rabbit's uterus test, and the blood-pressure test (using a small dog as the test animal) failed to give evidence of the presence of epinephrin in extracts of tumor metastases. In addition, the tumor and its metastases did not turn black on standing exposed to the air nor did extracts of tumor tissues assume a pink color when similarly treated, as tissues and solutions which contain epinephrin invariably do. It appears, therefore, that this tumor did not contain epinephrin. (The foregoing tests for epinephrin were made by Dr. Clyde Brooks of the Department of Experimental Therapeutics of the University of Chicago.)

In the gross, this tumor, excepting for the very extensive lymphatic metastases, presented most of the characteristics of typical hypernephromas. Under the microscope, however, a great variety of structural types — alveolar, sarcomatous or carcinomatous, angiosarcomatous or possibly peritheliomatous, all culminating in the predominatingly endotheliomatous metastases — are found. The inconstancy of the intercellular connective tissue network[29] in the alveolar portions of the growth, together with the coarse connective tissue trabeculæ with hyaline degeneration enclosing communicating clefts found in other portions, gives a further touch of the endothelioma.[30]

On a morphological basis the diagnosis of endothelioma, primary in the right adrenal, seems to be warranted. We cannot determine absolutely whether this tumor arose from the adrenal cortex or from the endothelium of the blood or lymph-vessels of the gland, although if one were to confine one's study to sections from the "rind" of the primary tumor one would be strongly inclined to adopt the former view. Accepting this hypothesis, we could call this tumor a mesothelioma of the adrenal, recognizing that such tumors, when of adrenal origin, present characteristics distinctly different from mesotheliomas of renal origin, excepting when the reversion to the embryonic "hylic" type, as defined by Adami,[31] i. e., pure sarcoma, has been complete in both.

29. Woolley: Bull. Johns Hopkins Hosp., 1903, xiv, 21.
30. American Text-Book of Pathology, 1902, p. 207.
31. Woolley and Adami: Tr. Assn. Am. Phys., 1902, xvii, 627.

Lasagna[3] recently described a malignant tumor of the adrenal which paralleled in structure to some extent the "rind" of the specimen considered above. In discussing the problem of diagnosis, Lasagna writes as follows:

> Thus, in our case we may not speak of carcinoma, or of sarcoma, in the strict sense; histologically there is a mixture of the two, a transition from carcinoma to sarcoma, or the reverse, such as one occasionally meets with in experimental tumor research. To-day one may not speak of mesothelioma, with Woolley, or of sarcoma, with De Paoli, or of hypernephroma with Borst, but only of adrenal tumors with typical or atypical characters.

It does not appear that Lasagna's reasons for refusing the diagnosis of "mesothelioma" are wholly justifiable, even in the light of the findings of experimental tumor research, for the term was intended to cover the very things because of which Lasagna rejects it: i. e., "transitional adenocarcinomas." Experimental research may in time demonstrate that the reasoning of Woolley and Adami from embryogenetic considerations does not apply, but such evidence is certainly not now at hand.

I am indebted to Dr. H. Gideon Wells of the University of Chicago, for the privilege of reporting this autopsy.

HEMOCHROMATOSIS

A REPORT OF THREE CASES AND A DISCUSSION OF THE PATHOGENESIS

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Hemochromatosis is the name given by von Recklinghausen[1] to a rare disease of metabolism, the etiology of which remains wrapped in obscurity. In the English literature there are few articles on this subject, which is one of great interest pathologically. Therefore, the three cases of this series are reported in detail with the impressions which I have derived from the study of them, in the hope that they may be of aid in the ultimate solution of the problem.

SUMMARY AND COMPARISON OF CASES

The three cases here reported afford an excellent opportunity for the study of the disease. The first case is one of simple hemochromatosis with the complication of tuberculous peritonitis forming a prominent part of the clinical picture. The other two cases are quite typical of the more frequently described form usually designated as bronzed diabetes. In all three cases there were the associated signs of asthenia, enlargement of the liver, and skin pigmentation which served to make the diagnosis clear in the two cases in which diabetes was present. In Case 1, without diabetes, the diagnosis was made more difficult by the presence of the tuberculous peritonitis, but in this case, too, the association of the signs just mentioned was considered very suggestive of hemochromatosis.

Alcohol cannot be cited as an important factor in the etiology of these cases, although none of the patients was a total abstainer. In Cases 1 and 3 there is a history of attacks of dysentery which occurred, however, at least ten years before there were any symptoms of hemochromatosis.

In none of the cases had the bronzing of the skin or the liver enlargement been noticed by the patient before entering the hospital. The skin pigmentation increased noticeably in all of them while under observation. Pigmentation of the mucous membranes was not present.

The onset in the first case was rather insidious. It was more abrupt in the other two, the first symptoms being those of diabetes. The duration of the disease in each case after the appearance of the first symptoms was twelve, ten and five months, respectively.

It is noteworthy that in Cases 2 and 3 there occurred a bilateral acute parotitis which persisted for only a few days and cleared up entirely

1. Von Recklinghausen: Ueber Hämochromatose, Tagebl. d. Versamml. deutsch. Naturf. u. Aerzte, 1889, p. 324.

before death. In Case 3, there was a terminal *Staphylococcus aureus* septicemia.

The blood-counts show normal numbers of red cells or a slight diminution.

The pathology of the three cases is essentially the same, with minor, though interesting variations. The omission of certain organs in the microscopic descriptions of each case is due to the fact that different tissues were available for study in the different cases. The liver, pancreas, spleen, thyroid, kidneys, adrenals and lymph-nodes are described in all three. In each case, studies were made of other organs which were not available in both the other cases. The iron-containing pigment, hemosiderin, is found in great abundance in the secreting cells of all the glandular organs examined, including the liver, pancreas, salivary glands, stomach, Brünner's glands, serous glands in the bronchi, trachea and larynx, thyroid, parathyroid, glomerular zone of adrenal, prostate, and in certain cells in the kidney. In addition, it appeared in the cardiac fibers, in the connective tissue of those organs after the disintegration of the parenchymatous cells, in the lymph-nodes, in the spleen in small amounts, in the bone-marrow, in certain cells of the cutis, in cartilage cells, and in the endothelium of blood-vessels, especially of the sexual organs.

The abnormal iron-free pigment, hemofuscin, is present in considerable quantities only in Case 3, and is here especially noticeable in the walls of blood-vessels and large ducts and in the capsules and trabeculæ of lymph-nodes.

In all the cases there is an increase in those pigments present in less degree physiologically. There is a striking accumulation of fine yellow pigment granules in the tubules of the testes and epididymes and in the vas deferens and seminal vesicles in the third case.

In each case there is an increase in the connective tissue of the liver, pancreas, lymph-nodes and spleen. In addition, this occurs to slight extent in the heart muscle in Case 2 and in the prostate and testicles in Case 3.

Case 2 suggests a slow deposition of pigment for a comparatively long time, while the picture in the third case gives one the impression of a rapid continuous process.

CASE 1.—*Medical No. 24,427. Simple Hemochromatosis without Diabetes. Tuberculous Peritonitis.*

C. M., a white man, a watchman, aged 55, was admitted to the Johns Hopkins Hospital, July 30, 1909, and died Sept. 5, 1909. Complaint: Pains in abdomen and frequency of micturition. Family history negative.

Past History.—The patient has with rare exceptions been well and strong. The periods of ill health, which he recalls most clearly, occurred during his residence in Cuba about ten years ago. He had the usual infectious diseases of childhood and, in addition, small-pox at 3 years of age, and malaria while in Cuba.

ten years ago. Following this malarial attack he was in a military hospital for three months.

Head.—Eyesight has been failing for the past eight years and more rapidly during the past twelve months.

Cardio-Respiratory.—Had some cough, otherwise negative.

Gastro-Intestinal.—Appetite has always been good; there is no nausea nor vomiting, no eructation of gas. Bowels rather irregular. While in Cuba, ten years ago, he suffered from an attack of dysentery during which his stools contained mucus and blood. This attack lasted about six or eight weeks altogether, with intervals of comparative freedom.

Genito-Urinary.—While in Cuba, before the malarial attack, the patient experienced considerable inconvenience from frequency of micturition. He passed large quantities of urine; was obliged to rise four or five times at night for this purpose. His face, legs and ankles became puffy and swollen. The polyuria has never entirely disappeared, but has never again been so marked as at that time.

He denies gonorrhea and syphilis.

Habits.—He drinks whiskey and beer in moderation, but does not get drunk. He has never done any heavy work.

Present Illness.—The onset was rather insidious. Patient says he has had more or less trouble for a year with increased frequency of micturition, passing small quantities of urine each time. There is no pain during the passage and the urine contains no blood. He has considerable abdominal pain, especially on coughing. This pain is not related in any way to the taking of food.

Physical weakness has been especially noticeable during the last three or four weeks. He cannot walk far without sitting down frequently to rest. He has some cough, but no shortness of breath. Bowels are irregular with alternating periods of constipation and diarrhea. The abdominal pain is especially severe on the right side after standing for some time.

Physical Examination.—The patient is a large man. The skin of the face is coppery-red in color, the vessels of the cheeks dilated, the left pupil slightly larger than the right. The breath is foul and the teeth in poor condition.

The skin over the neck and thorax is covered with small, reddish, elevated, discrete papules. The capillaries of the thorax are enlarged, especially in the lower part, where they form a striking band running across the lower front just above the costal margin.

The lungs and heart are normal.

The abdomen is distended and soft; the lateral veins markedly enlarged. There is tympany in the lower central portion, dull tympany and shifting dulness in the dependent flanks. No masses nor areas of tenderness can be demonstrated.

The liver is greatly enlarged; the dulness, beginning above at the fifth rib, extends 9 cm. below the costal margin where the edge is distinctly felt. In the midline it reaches a point half way between the umbilicus and the xyphoid cartilage.

The spleen is readily palpable 4 cm. below the costal margin.

Deep reflexes are demonstrable. The knee-jerk is more marked on the right.

Blood Examination.—August 6, red cells 5,100,000 per c.mm.; leukocytes 9,000; hemoglobin 105 per cent. (Sahli). The Wassermann reaction (blood serum) is negative.

Examination of the stomach contents reveals no special deviation from the normal findings.

On August 11, the pigmentation is noted as extreme over face, hands, forearms, areolæ of nipples, feet and legs, and of a deep coppery-brown color. There was no jaundice.

The patient's temperature, since admission, has ranged from 99 to 100 in the morning, and from 100 to 102 in the evening.

Examination of Stools.—On several occasions the stools were found to be small, semi-solid in consistence and of brown color. There were no macroscopic masses, no parasites, no mucus. The microscope revealed a normal picture. There was no occult blood.

On August 25, the abdominal distention had become so marked that paracentesis was performed and there were obtained 7,500 c.c. of a cloudy, straw-colored fluid, of which the reaction was neutral, specific gravity 1,015, albumin content 15 gm. per liter. The test for occult blood was positive. Microscopic examination of a centrifugalized specimen showed numerous red blood-cells, a few leukocytes and several large multinucleated cells.

At the second tapping, five days later, 550 c.c. of a similar fluid were obtained. A culture from this fluid remained sterile.

On September 2, the patient was drowsy and so weak that he could not feed himself. He complained of pain in the back, tightness of abdomen and difficulty in taking deep breath. The skin pigmentation had definitely increased and was of a bluish, cyanotic tint.

Blood-count showed 3,960,000 red cells, 12,000 leukocytes. A culture from the blood remained sterile. The Wassermann reaction was adjudged negative, though there was partial complement fixation.

The condition of the patient became gradually worse until his death in coma on September 5. During the last week the patient's temperature was intermittent, 97 to 101.

The blood-pressure fell during his stay in the hospital from 105 to 85 mm. of mercury.

Examination of Urine.—Soon after admission, the urine was pale orange in color; acid in reaction; specific gravity 1,023. It contained neither albumin nor sugar, but a few hyaline casts. In subsequent examinations there was occasionally a trace of albumin with hyaline and granular casts and several times there was an atypical and slight reduction of Fehling's and Nylander's solutions. There was never any fermentation with yeast, nor any acetone or diacetic acid present.

Clinical diagnosis was not definitely established. The picture was considered suggestive of hemochromatosis but the fever aroused suspicion of a tuberculous infection with adrenal involvement.

Autopsy No. 3,271 (performed 1½ hours after death).

Anatomical Diagnosis.—Hemochromatosis; pigmentation of liver, pancreas, lymph-nodes, gastric and intestinal mucosa, thyroid, parathyroids, adrenals, and skin over the face, hands and feet; cirrhosis of liver with slight collateral circulation; ascites; fibrosis of pancreas and lymph-nodes; acute tuberculous peritonitis with serohemorrhagic exudate; acute tuberculous pleurisy (right); tubercles in kidneys; atelectasis of lung; chronic purulent bronchitis; chronic passive congestion of kidneys; cloudy swelling of kidneys; cysts of the tunica vaginalis of the testicles; slight chronic fibrous myocarditis; adenoma of pancreas.

Body is that of a slightly emaciated white man, 177 cm. in length. There is an extreme dusky cyanosis of the face, which is only partially obliterated by pressure. After the blood has been expelled from the tissues by pressure, the skin over the face and neck still remains markedly pigmented. This pigmentation has a dusky grayish-brown appearance, resembling to a slight extent that found in argyria. It is very marked over the face and neck; is also found over the hands and forearms, fading gradually toward the elbows, and over the feet and legs becoming less marked towards the thighs. The skin over the entire body is slightly pigmented.

The teeth are carious and there is marked pyorrhea alveolaris.

The abdomen is much distended with distinct bulging of the flanks. The genitalia are slightly pigmented, but here the pigment is not very marked. The fat of the abdominal wall is scanty and the muscles atrophic. On opening the abdominal cavity there escapes about 6 liters of a blood-stained, amber-colored fluid which contains numerous flakes of fibrin. Over the serous surfaces of the

intestines one finds, everywhere, small flakes of fibrin which dull the surface to a slight extent. On separating the intestinal loops from each other the folds of the mesentery are seen to be covered with small, transparent, dew-drop-like nodules only a few millimeters in diameter, alternating with larger more opaque nodules. Between these nodules the serous surface is extremely hemorrhagic so that it has a mottled, reddish and grayish, roughened appearance. This lesion is wide-spread and is especially marked over the parietal peritoneum in the flanks and on the diaphragmatic surface. The surfaces of the pelvic viscera and of the liver and spleen present a similar picture in a less degree. The omentum is everted so that it lies beneath the costal margin extending from one parietal wall to the other without being attached to either. It is short, much thickened, cuts with difficulty and shows throughout numerous hemorrhages.

The liver extends 5.5 cm. below the top of the ensiform in the median line and just reaches the costal margin in the mammillary line. The stomach is slightly dilated.

On removing the sternum, the fat of the anterior mediastinum is found to have a chocolate-brown appearance. There are numerous lymph-glands found in this region which are enlarged and more intensely pigmented than the fat. Most of the glands are slightly firmer than normal and cut with resistance.

The pleural and pericardial cavities are normal.

The *heart* weighs 320 gm. The cavities and the valves are practically normal. The musculature of the right ventricle shows a slight mottling suggestive of the faded leaf appearance. The heart muscle of the left ventricle is slightly mottled and shows a slight diffuse increase in fibrous tissue. No marked pigmentation is appreciable in gross.

Both *lungs* show a definite purulent exudate in the smaller bronchioles and a moderate emphysema except in the lower portions, which are atelectatic. On the pleural surface of the right lung there are numerous small, grayish nodules, apparently fresh and surrounded by a slight hemorrhagic zone.

The *spleen* weighs 570 gm., and measures 21 by 11 by 7 cm. Its capsule is firmly attached to the diaphragm by a mass of adhesions which are torn with difficulty. The surface elsewhere is covered with the exudate already described. The spleen is quite firm. On section one finds the architecture very distinct. There is a marked increase in fibrous tissue. Multiple sections show here and there nodules, which measure twice the size of the average Malpighian corpuscle and which are distinctly yellow and soft.

The *stomach* and *duodenum* are somewhat distended, and the mucosa of each viscus is definitely pigmented or stained by a black viscid fluid which is present in large amounts. This material has a fecal odor and suggests regurgitation of intestinal contents. The gastric mucosa is considerably congested. A few small hemorrhages are seen along the rugæ. There are a few dilated venules beneath the mucosa of the esophagus near the cardiac orifice.

The *pancreatic* and *common bile-ducts* empty separately into the duodenum. Their orifices are separated only by a thin wall of mucous membrane. Both ducts are patent throughout.

The *pancreas* presents a very remarkable appearance. Its surface is of a pale chocolate color. The head is relatively large, although apparently not quite so large as normal. The remaining portion of the organ is small. The lobulation is distinct. On section the color of the parenchyma is found to be of a deeper brown color than that of the surface. There is some infiltration of fat between the lobules, but there does not seem to be a great excess of fibrous tissue. There are small grayish spots about the size of a pin head, which are relatively slightly pigmented.

The *liver* is also very striking. It measures 28 by 18 by 9.5 cm. and weighs 1,650 gm. Its surface is quite irregular, small knobs of parenchyma sticking up everywhere between coarse bands of fibrous tissue which are markedly depressed. The color is a deep brown, but on the liver the pigment is not as striking on the surface as on the pancreas and lymph-nodes surrounding it. The liver is

extremely firm and is cut with marked resistance. The cut surface has a rather striking brownish pigmentation. The normal lobulation is absolutely destroyed. Bands of fibrous tissue varying much in size run through the entire liver tissue dividing it into larger and smaller lobules quite different from the normal structure. The fibrous tissue in many places is stained with bile.

The *gall-bladder* is dilated and contains a large amount of tenacious, tarry bile.

The *right kidney* measures 11 by 5.5 by 4.5 cm. The two kidneys weigh 260 gm., are somewhat congested, and show a few small tubercles.

The *urinary bladder* is small and atrophic. Its mucosa is slightly congested, but otherwise normal.

The *prostate* shows no abnormality.

The *testicles* are atrophic. There are a few small cysts in the tunica vaginalis, which contain a clear fluid.

The *seminal vesicles* seem normal.

The *rectum* is extremely congested and shows numerous hemorrhoids.

The *duodenum* is thickened. Its mucosa is edematous and slightly bile-stained. The entire *intestinal mucosa* shows a deep grayish discoloration.

The retroperitoneal lymph-nodes seem to be very numerous. They are all enlarged and show the same chocolate brown pigmentation described for those in the mediastinum.

Of the neck organs, the *esophagus* is normal except for a slight congestion and the varices found in its lower portion. The thyroid is slightly enlarged, and although the pigment here is less conspicuous than that found in other organs, there is a definite brownish discoloration.

TECHNIC

For histological detail, tissues fixed in Zenker's fluid were cut in paraffin and sections stained with hematoxylin and eosin.

For the microchemical demonstration of iron, various methods were used. Among these may be mentioned Perl's reaction, the conversion of the iron into Prussian blue by treating sections with a 2 per cent. solution of potassium ferrocyanid and 1 per cent. hydrochloric acid; treatment with ammonium sulphid; and a combination method described by Nishimura[2] working in Kaiserling's laboratory. This last method gave the best results. According to Nishimura's experiments, ammonium sulphid reacts with firmly bound iron compounds which are not affected by Perl's method. The latter, however, gives a much better picture than that produced by the black iron sulphid, especially in the presence of other than iron pigments in the same section. He, therefore, first converts the iron into the sulphid by treating with strong ammonium sulphid for one hour and then subjects the sections to a mixture of 2 per cent. potassium ferrocyanid and 1 per cent. hydrochloric acid in equal parts for one hour, after which the sections are washed in 0.5 per cent. hydrochloric acid followed by distilled water. The sections are then counterstained with carmin.

This procedure gives an excellent and uniform method for the demonstration of iron and is perhaps improved by shortening the time of exposure to the mixture of ferrocyanid and hydrochloric acid to twenty minutes, since, according to A. B. Macallum, this mixture decomposes at the end of that time and is apt to give the tissues a diffuse light blue stain.

Alcohol or formaldehyd solution fixation is generally considered preferable in the study of these pigments and all the reagents used should be fresh.

MICROSCOPICAL EXAMINATION

Liver.—The striking features are excessive deposits of golden-brown pigment granules in the parenchymatous cells and in the connective tissue; a well-marked

2. Nishimura: Vergleichende Untersuchungen über die microchemische Eisenreaktion in menschlichen Lebern, Centralbl. f. allg. Path. u. path. Anat., 1910, xxi, 10.

cirrhosis; and evidence of regeneration in the occurrence of clumps of large, rather slightly pigmented, apparently new liver cells. The normal lobulation is obscured and a new architecture formed by the bands of connective tissue running in different directions throughout the organ and dividing it into lobules of various shapes and sizes.

The liver cells vary widely in size and staining properties in different areas, though these areas may be situated side by side. Almost all contain in striking abundance granules of a golden-brown pigment. Some cells appear to be fairly bursting with this load but even in these extreme cases the nuclei can be seen though staining faintly. The most characteristic cell has a well-staining proto-

Fig. 1.—Liver (Case 1). Low power. Iron pigment had been converted into Prussian blue by Nishimura's method and appears black in the figure. Note the heavy accumulation in the connective tissue (*x*) and the relatively heavy deposits in the periphery of the three liver lobules shown rather than in the center (*a*).

plasm and nucleus with a fair amount of pigment gathered in granules near the center at the furthest point from the blood capillaries as pointed out by Opie[3] and others. Only in the few nodes of larger, more deeply staining, fresh appearing liver tissue are there any pigment-free cells. The cells in the periphery of these areas may be deeply pigmented, but in the larger central area, only the

3. Opie: A Case of Hemochromatosis. Tr. Assn. Am. Phys., 1899, xiv, 253.

stellate cells of von Kupfer show the pigment granules. In general, the cells in the centers of the lobules are the least affected, the pigment increasing in amount as the periphery of the lobule and the connective tissue septa are approached (Fig. 1). Where the amount of pigment is increased and the granules crowded together, there is a tendency toward the larger size of the individual pigment body with the formation of globules measuring several microns in diameter.

The fibrous tissue varies much in density in different places; hence, presumably, in age. The greater part and that in closest relation to the disintegrating liver cells is quite loose and cellular and contains many pseudo-bile-ducts. Here the pigment is scattered more uniformly and in smaller granules or globules than in the older, denser, narrower, fibrous strands further removed from the liver cells. The epithelium of most of the numerous pseudo-bile-ducts is heavily loaded with very finely granular yellow pigment, only some of the cells near the end having escaped. The walls of all vessels contain masses of pigment and the endothelium of the veins, both hepatic and portal, show fine yellow granules in abundance. The cells of the peritoneal covering of the organ, where they are preserved in the sections, are swollen and pigmented with finely granular yellow material. Immediately beneath the serous membrane the connective tissue is increased, in places amounting to thick scars in which large bile-ducts are strikingly numerous. None of these ducts are heavily pigmented and many escape altogether. This corresponds to areas described by Hess and Zurhelle[4] as the adenomatous stage in the growth of the bile-ducts. In their case, too, the pigmentation in these areas was slight.

Practically all the pigment in the liver reacts positively for iron by Perl's Prussian blue test. That in the liver cells, connective tissue, endothelium of vessels, etc., stains quite uniformly, varying in shade with massing of the granules. Only in the pseudo-bile-ducts does the pigment seem to vary in its reaction to the test. Here most of the granules become blue, others bluish-green, a dirty green, or are entirely unaffected. Hess and Zurhelle record these differences as occurring quite widely in their sections and consider them no indication of important distinctions in the pigment. They suggest that the youngest pigment stains bright blue, and, increasing in age, passes through the various stages mentioned, the oldest remaining unstained. This observation and the interpretation as given tend strongly to support the view that these so-called pseudo-bile-ducts are evidences of degeneration rather than regeneration of the liver cells.

Pancreas.—There is distinct though slight cirrhosis of the pancreas, both interlobular and interacinar, which at first glance seems of greater extent because of the deposits of fat, especially in the interlobular tissues. Neither process has become excessive. The connective tissue, everywhere, contains a considerable amount of pigment scattered in its interstices or tightly packed in connective tissue cells. In some areas the new fibrous tissue is quite cellular, containing many well-preserved nuclei, the remnants of parenchyma cells, and many small globules of pigment.

The same golden-brown pigment seen in the liver is deposited to a less extent in all the structures of the pancreas and relatively heavily in the islands of Langerhans, which are large, well defined and quite numerous in all parts of the organ examined. Indeed, in sections stained with hematoxylin and eosin, the heavily pigmented, more lightly staining large islands are the most prominent parts of the field (Fig. 2). The prominence of the pigment granules is, in part, due to the greater contrast between the brown of the pigment and the lighter staining protoplasm of these cells; but that it is not entirely so explained is shown by the Perl stain. Many of the islands contain more blue than the surrounding tissue, and others show a pale background of non-pigmented cells on which stands out a single strand or coil of cells near the center, loaded with blue granules. The cells of the islands are large and well formed and for the

4. Hess and Zurhelle: Klinische und pathologisch-anatomische Beiträge zum Bronzediabetes, Ztschr. f. klin. Med., 1905, lvii, 344.

most part have well-preserved nuclei, though some of them are loaded to the fullest capacity with pigment. Occasionally may be seen an irregular, dark staining mass in the place of the nucleus, perhaps one or two in each island. This nuclear change is more prominent in the main parenchymatous cells, occurring diffusely throughout the sections, sometimes involving several cells in one acinus and again only a few in a whole lobule. These cells vary in size, somewhat in shape and very greatly in their pigment content. Not all the cells are pigmented, but in each small lobule some acini are more or less affected. The pigment may be scattered in fine, almost imperceptible grains throughout the cell protoplasm or may distend the cell membrane and displace the nucleus with large granules crowded closely together. The cell protoplasm, where not obscured by pigment, is seen by high power to contain fine vacuoles. Besides the karyorrhexis already noted, a few of the cells show very faintly staining nuclei. Only the smaller ducts contain pigment in their lining cells. Most of the pigment in the sections reacted strongly for iron by the Perl test. There is a very small

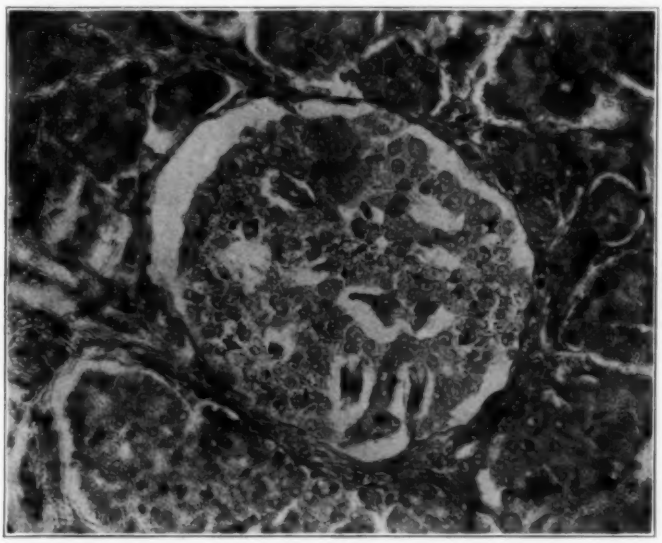

Fig. 2.—Pancreas (Case 1). Hematoxylin and eosin. Note the pigment granules in the island of Langerhans, the thickened capsule and the pigment in the surrounding pancreatic cells.

amount of finely divided yellowish pigment in the walls of some of the vessels which does not give the iron reaction. This corresponds to the hemifuscin of von Recklinghausen in contradistinction to the iron-containing hemosiderin.

Many polymorphonuclear leukocytes, as well as mononuclears, are seen in the blood-vessels, and wandering out in the connective tissue septa. Though carefully searched for, no focal necroses were seen. There are no cells in the lumina of the ducts.

One section passes through a small adenoma about 0.5 mm. in diameter, which resembles an enormous island of Langerhans. It has a distinct fibrous tissue capsule from which septa with vessels enter the tumor. The cells are large and similar in all other respects to those in the islands of Langerhans. Only a few scattered cells contain pigment granules.

Spleen.—There is some increase in connective tissue. Pigmentation is not conspicuous in sections stained by ordinary methods due to the similarity in the color of the granules and the large numbers of red blood cells present in the splenic pulp.

With the Prussian blue method a slight amount of pigment is demonstrated lying along the sinuses, and a few grains here and there in a Malpighian body. The granules are small and are present in rather large phagocytic cells. All the pigment reacts well to iron tests.

The venules are distended with blood. The individual cells differ slightly in size and shape.

The Malpighian corpuscles average about 0.3 mm. in diameter. In several of these and once or twice in the pulp there are seen areas of necrosis with a diameter of about 0.2 mm. They are rather sharply defined, contain a grayish, granular, necrotic-looking material with scattered nuclear remnants. There is very little reaction in the surrounding tissue.

Thyroid Gland.—This shows marked pigmentation. Apparently every cell of every alveolus contains innumerable golden-brown granules. The distribution is remarkably uniform, more so than in the other tissues described. The majority of the cells are affected to the same degree, but here and there are found a row of cells distended and closely packed with pigment and a few of the alveoli contain only a few grains in each cell. The nuclei are well preserved and show no sign of degeneration even in the most heavily loaded cells. The alveoli are natural in size and shape; the colloid is slightly decreased in amount. The connective tissue is practically free from pigment. Only by careful search can a few large grains or, rather, small globules be found in a branching connective tissue cell or free in a lymph space. The blood-vessels, large and small, are distended with blood, the tissues are forced apart by edema, and many free red blood cells are seen in the meshes of the connective tissue. Leukocytes are not prominent, but may be seen occasionally, and here and there one has worked its way in among the pigmented alveolar cells. With the Perl test the pigment reacts positively for iron, but requires longer exposure to the reagents. There is more of the dirty bluish-green color than is usually observed elsewhere. Very little, if any, remains unchanged.

Parathyroid.—Cells with eosin-staining granular protoplasm greatly predominate over the clear non-staining variety. Small colloid vesicles are occasionally seen. There are many pigmented cells scattered throughout the gland. The pigment occurs in fine yellow grains and reacts readily for iron. Most of the pigmented cells are those having a clear non-staining protoplasm.

At one end of the gland there is a cyst measuring about 3 mm. in diameter, almost as large as the remainder of the parathyroid. It contains a heavy, granular precipitate and is lined by a single row of cubical cells having a clear protoplasm. The nucleus, as a rule, is vesicular; in some cells, it is pyknotic with very irregular edges. Many of the cells lining the cyst contain the iron pigment.

Kidney.—There is a very slight grade of chronic nephritis with small increase in fibrous tissue and cloudy swelling of the secreting epithelium. The blood-vessels throughout the sections, glomeruli, and interlobular capillaries of cortex and medulla are congested. The amount of pigment is small, compared with that in the organs just described, and its distribution quite patchy. It occurs as rather large granules in considerable amount if present at all. It does not occur in isolated grains or even a few scattered grains here and there. The sites of predilection are the collecting tubules first, and occasionally, the loops of Henle. It gives the iron reaction readily. No pigment is found in the walls of the blood-vessels or elsewhere in the connective tissue.

Adrenal.—The pigmentation usually seen in the reticular zone of the cortex is much increased, being found in almost all the cells of this layer as scattered granules of light brownish color. Here and there in the outermost cells of the

glomerular zone, the nuclei are surrounded with a very similar pigment in fine granules of quite uniform size and of a slightly darker color than that in the inner layer; for the latter appears brighter even in much larger amounts. With the Perl test most of the glomerular pigment reacts positively, but not completely. Usually the cell protoplasm stains a diffuse blue in which the granules appear as dark green. The reticular pigment remains quite unchanged. Scattered through the medulla may be seen an occasional pigmented cell and a few of these react positively for iron. There was no tissue fixed for study of the chromaffin system.

The lipoids of the cortex were less than is usually found. Their solution leaves the cells of good shape and staining qualities.

Lymph-Nodes.—All sections show heavy pigmentation and increase in connective tissue. The pigment in different sections varies somewhat in situation. As a rule, the sinuses and peripheral parts of the follicles contain almost all of

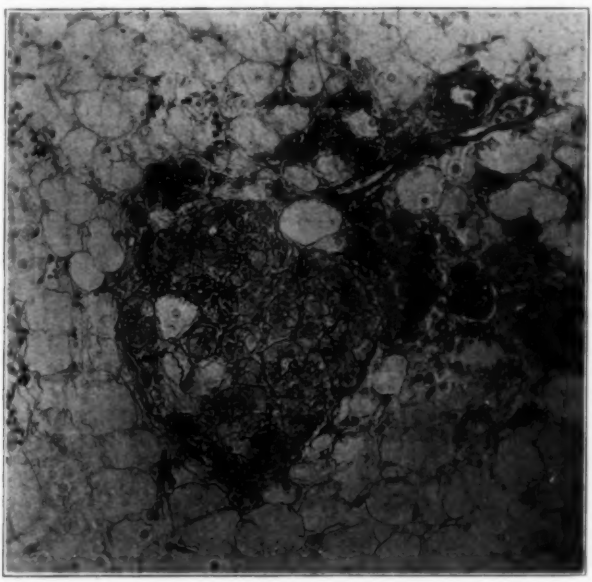

Fig. 3.—Pancreas (Case 2). Hematoxylin and eosin. Low power. Note the preponderance of fat in the field; the heavily pigmented and sclerotic condition of the pancreatic tissue shown in the right center; and the mass of clear non-staining cells, showing fewer pigment granules.

the pigment, but occasionally, a whole follicle is loaded with it while the surrounding sinuses are relatively free. It occurs in rather large globules, 4 or 5 microns in diameter, which fuse to form larger masses, and lie either free in the interstitial spaces or in phagocytic cells of various kinds. Very often the character of the containing cell is obscured by the amount of pigment present. In other cases they resemble the polyblasts of chronic inflammation. Phagocytic giant cells with two or three nuclei are not uncommon, and occasionally, there are seen large syncytial masses, 80 to 100 microns in diameter, having fifteen or twenty nuclei and enclosing several large clumps of pigment.

The connective tissue is increased, especially between the sinuses, where it forms fairly thick trabeculæ. Here and there it is found invading a heavily pigmented follicle or growing out from its central artery. The pigment takes a dark blue color in the iron test whether the ferrocyanid or ferricyanid of potassium is used.

In one of the nodes examined there are three or four young tubercles composed of the typical epithelioid cells and surrounded by lymphocytes. There is no pigment in the tuberculous tissue.

Lung.—The sections show a moderate emphysema, thickening of the smaller vessels, a considerable quantity of coal pigment and a very few conglomerate tubercles of the proliferative type. There is no other pigment than that of anthracosis.

Omentum.—The omentum shows extensive extravasation of blood which occurs in masses throughout the sections together with an exudate of fibrin, mononuclear cells and few polymorphonuclear leukocytes. Scattered uniformly through the exudate are seen typical discrete and conglomerate miliary tubercles with epithelioid, small mononuclear and giant cells.

The parietal peritoneum shows rather acute tuberculous peritonitis with a considerable amount of extravasated blood. There is no pigment in the striated muscle shown in this tissue. The exudate on the visceral layer over the kidney is very similar but contains less blood. The perirenal fat shows many large dilated blood-vessels.

CASE 2.—*Medical No. 20,197. Hemochromatosis with Diabetes; Onset with Diabetic Symptoms Ten Months Before Death.*

D. C. K., white man, a grocer, aged 37 years, entered the Johns Hopkins Hospital September 26, and died Oct. 22, 1906.

Complaint.—Lack of strength and stomach trouble.

Family History.—Negative.

Past History.—The patient has always been robust with the exception of measles, mumps and whooping-cough during childhood and an attack of chills and fever about twenty years ago.

Habits.—He is accustomed to drink three cups of coffee each day, uses tobacco moderately and drinks not more than one glass of beer a week.

Genito-Urinary.—There was no urinary disturbance before the present illness. He denies syphilis and gonorrhea. He has been married ten years and has three children.

Patient has had hemorrhoids for five or six years.

Present Illness.—This began about nine months ago with a severe cold which left the patient with a tired feeling. This cold lasted about one month during which the patient noticed that he was drinking large amounts of water and getting up several times at night to pass urine of crystal clearness. His appetite was then moderate. He had been "excited" but not "worried" over business affairs two or three weeks previous to the polyuria. He began to experience about this time a marked feeling of weakness; he could work no more than fifteen minutes, consecutively.

In July he went to a Cincinnati hospital where his hemorrhoids were cured after three operations. Here he was also placed on a diet, but continued to lose weight.

Since then his appetite has greatly increased; his skin is dry; stools clay-colored; and he has become constipated.

About ten days ago sharp pains developed all over the body, moving from one part to another, and after several days subsided into a dull, aching pain aggravated on motion.

Physical Examination.—The patient is a well-built, poorly nourished man. His skin is harsh, brawny and dry without a trace of perspiration. The face

has a fairly good color. There is no jaundice. The pharynx and soft palate are red, dry and leathery; strings of mucus project down from the posterior nares. The skin of the neck and thorax is negative.

The heart and lungs are normal.

Abdomen.—The liver is enlarged, the relative hepatic dulness begins at the upper border of the sixth rib and extends 4 cm. below the costal margin where the edge is definitely palpable.

The spleen is not felt.

There is no general glandular enlargement.

The knee-jerks are present. The left knee is painful and appears to be slightly swollen, but measures the same as the right knee.

Blood Examination.—September 27, red cells 4,458,000; leukocytes 5,400; hemoglobin (Tallqvist) 90 per cent.

For examination of the urine see Table 1. On admission the urine contained 6.5 per cent. sugar.

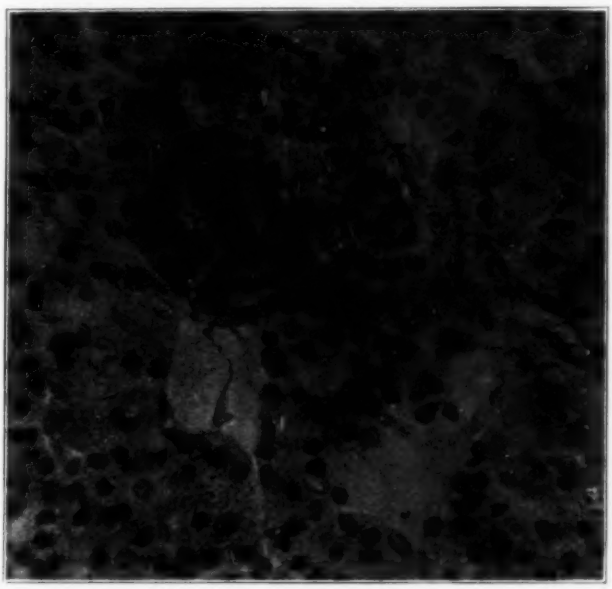

Fig. 4.—Parathyroid (Case 2). High power. Hematoxylin and eosin. Note the fine granules of pigment in all the cells and the many irregular, dark nuclei.

The patient became gradually more drowsy and apathetic until on October 11 the breath had a distinct odor of acetone and the appetite entirely failed.

On October 16, the patient was seen by Dr. Futcher, who noted that the most striking feature was the very marked grayish-brown bronzing of the hands and lower thirds of the forearms. This was also apparent, but to a less extent, on the face and neck and over the shins, especially the right one. There was no increase of pigmentation in the axillæ or about the nipples or genitalia. The sclerotics and the buccal mucosa were also free from pigment. There was one definite petechial spot on the upper third of the right shin.

The right parotid gland was quite markedly swollen, tense and tender on pressure.

While there was no definite pigmentation of the skin of the body, the color seemed to be a little deeper than normal.

The parotitis cleared up within a few days.

The temperature was subnormal continuously.

The patient died in coma October 22.

Clinical Diagnosis.—Hemochromatosis; diabetes mellitus; acute parotitis; diabetic coma.

TABLE 1.—URINARY FINDINGS, CASE 2

Date.	Total Amount of Urine in c.c.	Specific Gravity.	Sugar — Per Cent.	Sugar — Gm.	Acetone.	Diacetic Acid.	Diet.
9/29	3,000	1.032	6.5	195.	..	..	Ward diet.
9/30	1,200+	....	7.2	86.4+	..	..	Ward diet.
10/ 4	2,600	1.040	4.4	114.4	..	..	Carbohydrate-free, plus one slice of bread.
10/ 5	1,980	....	4.6	91.	..	..	Carbohydrate-free.
10/ 6	2,630	....	3.7	97.3	..	..	Carbohydrate-free.
10/ 7	1,560	....	4.4	68.6	..	..	Carbohydrate-free.
10/ 8	3,020	....	3.9	117.7	..	..	Carbohydrate-free.
10/12	2,290	....	3.3	75.5	+	+	Carbohydrates renewed, plus soda bicarbonate.
10/13	3,480	....	7.2	250.5	+	+	Carbohydrates renewed, plus soda bicarbonate.
10/15	4,740	....	4.	189.6	+	+	Carbohydrates renewed, plus soda bicarbonate.
10/16	2,240	....	..	....	+	+	Carbohydrates renewed, plus soda bicarbonate
10/17	2,140	....	..	....	+	+	Carbohydrates renewed, plus soda bicarbonate
10/19	3,000	....	5.	150	+	+	Carbohydrates renewed, plus soda bicarbonate
10/20	2,820	1.030	2.6	73.3	+	+	Carbohydrates renewed, plus soda bicarbonate.
10/21	1,050+	1.029	2.5	26.2+	+	+	Milk ℥xlviii
10/22	2,120+	1.025	2.6	55.1+	..	..	Nothing retained.

Autopsy No. 2,782 (performed one-half hour after death).

Anatomical Diagnosis.—Hemochromatosis; pigmentation of liver, pancreas, heart, stomach, thyroid, parathyroids, adrenals, lymph-nodes, trachea and skin; chronic interstitial pancreatitis; cirrhosis of liver; chronic splenic tumor; cardiac hypertrophy and dilatation; chronic passive congestion of abdominal viscera; edema of intestines; ascites; degeneration of renal epithelium; hydrothorax and atelectasis of lungs; atrophic testes.

Body is that of a stoutly built man, 180 cm. in length. The subcutaneous fat is small in amount. On opening the peritoneum a large quantity of clear fluid is found, perhaps 2 liters; this examined by Dr. Emerson shows large quantities of sugar. The abdominal organs are in general normally disposed. The intestines are distended, and their walls thick and rather pasty. The peritoneal surfaces are smooth and glistening. The omentum is thickened and adherent here and there to the diaphragm and parietal peritoneum; and in the adhesions there are numerous, large, tortuous veins. These are also abundant in the mesentery but are not especially conspicuous about the round ligament of the liver. The liver does not extend below the costal margin. It is greatly distorted and shows deep fissures about its edge, especially near the gall-bladder. The distended gall-bladder is bent on itself and adherent to the edge of the liver. The spleen is greatly enlarged and not bound by adhesions. The diaphragm reaches the third rib on the right side and the fourth space on the left side.

The pleural cavities contain a small amount of fluid—about 250 c.c. on each side. The surfaces of the lungs are quite smooth and glistening. There are no

adhesions. The pericardial cavity contains very little fluid. Its surfaces are smooth.

The *heart* is somewhat enlarged, weighing 350 gm. The valves and orifices are normal. The root of the aorta shows some small plaques of elevation, and the coronary arteries are similarly flecked with small patches. The heart muscle is, in general, firm. The left ventricle is distinctly dilated. The muscle shows through the endocardium as a rather chestnut brown substance which is very much mottled with lighter and darker areas in the papillary muscles. This is practically the appearance seen in fatty degeneration, but it is not marked on section of the heart. On section the heart muscle shows the same chestnut-brown color throughout, but it is distinctly paler and more translucent toward

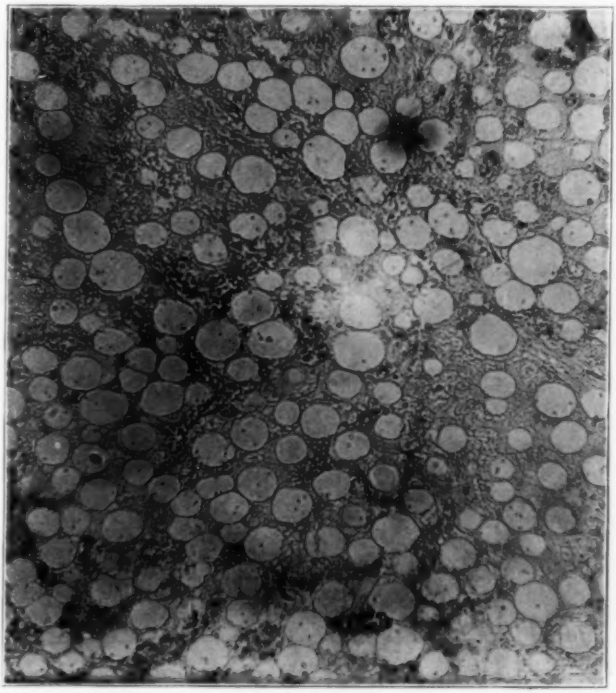

Fig. 5.—Bone-marrow (Case 2). Low power. Hematoxylin and eosin. Note the preponderance of fat tissue over the hematopoietic elements. This particular field contains more islands of blood-forming cells than the average.

the inner layer. The muscle of the right ventricle shows the same bright brown color.

The left *lung* shows some atelectasis at the base. The bronchial glands are blackened by coal pigment but not enlarged. The right lung shows a small flat scar at the apex. The bronchial glands are here distinctly brown. Another gland, also on the bronchus, which contains a quantity of black pigment, shows the brown only indistinctly.

The *spleen* weighs 300 gm. and measures 15 by 10 by 5.5 cm. In consistence it is somewhat flabby. On section the splenic substance is dark brownish-red, but

the brownish cast is very slight. The trabeculæ and vessels are distinctly visible. The Malpighian bodies are not enlarged, but are easily seen.

There is a minute accessory spleen at the hilum of the spleen and several pigmented lymph-nodes.

The *duodenum* is normal except perhaps for a slight reddening and swelling of the mucosa. The bile can be squeezed slowly from the bile-ducts.

The *stomach* contains only a little mucus. Its wall is corrugated and swollen, dark red, and the mucosa is seen thrown up into thick folds, which are very rough. The veins about the esophagus are not especially dilated.

Along the lesser curvature of the stomach there are several quite large lymph-nodes, which are brilliant, ochre-brown in color. On section the lymph-cords are visible as clear grayish nodules, while the remainder is opaque and yellowish-brown. Some of the nodes are red and show minute masses of pigmentation,

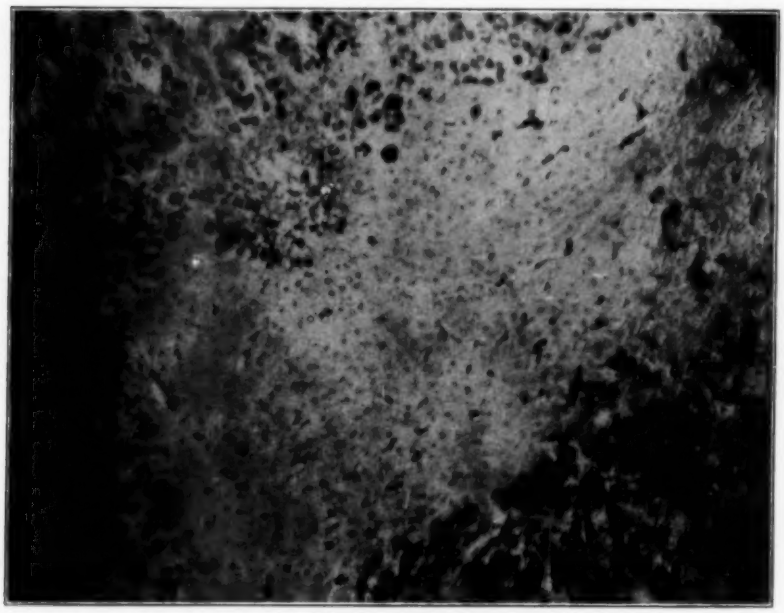

Fig. 6.—Liver (Case 3). Low power. The iron-containing pigment had been changed to Prussian blue by Nishimura's method and appears black in the figure. The section was counterstained in carmin. Note the zone of recently regenerated liver cells containing no pigment, except in the Kupfer cells. The older, surrounding liver tissue is heavily pigmented.

while others are uniformly dark brown. It seems possible that the non-pigmented nodes may be newly formed. The lymphatic channels leading to and from these nodes are greatly distended with clear and sometimes blood-stained fluid. The mesenteric nodes are not especially enlarged; they are much less pigmented, but there is a quite distinct coloration of the cortical layer.

The *pancreas* weighs 150 gm. It is large, firm, and measures about 19 by 4 by 2 cm. It is somewhat bound by adhesions to the surrounding tissues, in which there are many large pigmented lymph-nodes. The ducts are quite patent and contain no calculi. Their walls are about normal in thickness. The gland, on

section, is curiously mottled, portions of it quite irregular in size and firm, having a bright brown color, while the remaining intervening parts have the appearance of very solid fat. This is much firmer than ordinary fat and there is evidently a considerable amount of fibrous tissue running through it. The yellow fatty areas form a much greater proportion of the head of the pancreas than of the tail. In the brown areas, especially in the tail, the lobulation is extremely indistinct. Pale grayish dots are frequently seen which suggest the islands of Langerhans. From the surface the mottled appearance of the pancreas, with its alternating brown and yellow tissue, is very striking.

The *liver* weighs 2,400 gm. and measures 27 by 24 by 11 cm. It is very hard and its surface is extremely rough and knobbed. At the gall-bladder, the contractions of the liver in deep furrows is especially marked. On section the cut surface has a bright brown color. There is a very distinct lobulation, the nodular

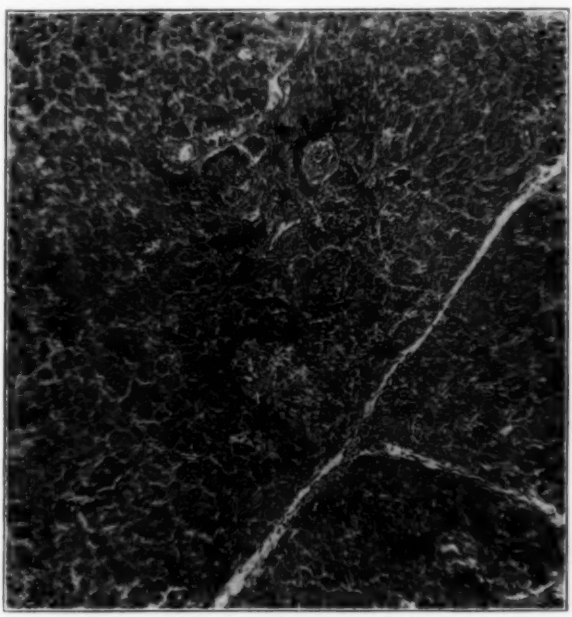

Fig. 7.—Pancreas (Case 3). Low power. Hematoxylin and eosin. Note the especially heavy accumulations of pigment around the three islands of Langerhans.

masses being separated by retracted, translucent bands. The lobules are fairly homogeneous in size, although there are some areas in which the scar tissue contains numerous very minute lobules. In many areas this lobulation seems to follow the normal very closely, the peripheral part of each lobule being paler, while the central part appears as a reddish dot. But there is great irregularity, and in other places the masses of liver tissue 2 mm. in diameter probably correspond in no way to the normal liver lobule, although they stand out sharply. At one point there is a distinctly outlined, round, yellow mass about 1 mm. in diameter.

The *peritracheal lymph-nodes* are not markedly pigmented, although the larger ones do show some abnormal coloration.

There are four *parathyroids* which are normal in appearance.

The *thyroid* is firm, possibly slightly browner than normal, and contains a considerable amount of colloid.

The mucosa of the *esophagus* seems normal. There are no varicose veins.

The mucosa of the trachea and of the epiglottis seem distinctly pigmented, mottled with yellowish patches.

The *aorta* is, in general, smooth, but shows some yellowish plaques of sclerosis. These are of small size and perhaps more abundant in the carotid arteries.

The *adrenals* are alike. The cortex is distinctly marked out, pale and sprinkled with opaque, yellow dots. The medulla is grayish brown.

The *kidneys* weigh 430 gm. The right kidney measures 14 by 7.5 by 5 cm. The two kidneys are quite similar in appearance. The capsule strips easily, leaving a surface somewhat roughened by depressions and on which the stellate veins are conspicuous. The surface is pale, pinkish-white, with a yellow cast. Minute dots of yellow opacity can be seen everywhere on the surface and minute hemorrhages are abundant. There are also translucent points. On section

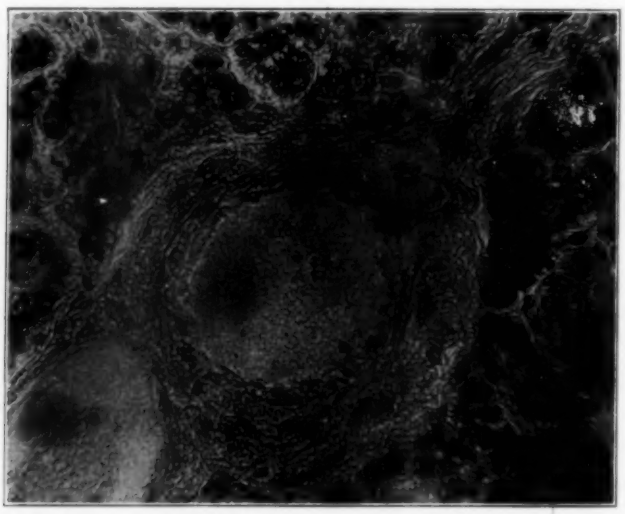

Fig. 8.—Pancreas (Case 3). High power. The iron-pigment had been converted into Prussian blue and the section counterstained with carmin. Note the granules of hemofuscin (yellow in the preparation) in the wall of the vessel and the dark hemosiderin in the surrounding pancreatic cells.

the cortex averages 7 mm. in thickness. The striations are quite straight. The central translucent rays are very distinct. The labyrinthian portion is very opaque and pale, the glomeruli standing out conspicuously as bright red points.

The solitary nodules are conspicuous throughout the large *intestine* and the mucosa is markedly edematous. Peyer's patches in the small intestines are swollen. The mucosa is not distinctly pigmented; in fact, it is quite pink. The upper portion of the small intestine is very much congested and of a purplish color. The edema persists throughout.

MICROSCOPIC EXAMINATION

Liver.—There is a well-marked cirrhosis, with rather dense bands of connective tissue intersecting and dividing the liver into lobules. These lobules are

very much larger than the normal liver unit and, in them, the cells are not arranged with the same regularity. Only rarely can a central vein be made out among the liver cells; almost always they are surrounded by connective tissue, and in this respect do not differ from those of the portal system.

The pigment is abundant and very striking in certain places. As a general rule, the liver cells contain about the same amount, closely grouped in golden-brown granules around or at one side of the nucleus and of such quantity as to occupy about one-third or one-fourth of the cell. This is the general rule, but in many places, scattered throughout the tissue, are seen areas having a diameter of ten or a dozen liver cells, which are filled with pigment, contained, for the most part, within the cells, but also found in smaller amounts free in the tissue. These cells are alike in resembling masses of pigment surrounded by a limiting cell membrane, but differ in the appearance of the nucleus, which in a few is the large round vesicular nucleus of the liver cell, and in the majority an

Fig. 9.—Heart muscle (Case 3). High power. The iron-containing pigment appears black in the figure. Stained by Nishimura's method.

elongated or oval, darker staining variety resembling more nearly that of a connective tissue cell or polyblast. There are also seen here and there smaller masses of pigment between the liver cells contained in the cells of von Kupfer or polyblasts inside the blood capillaries. The larger lobules of liver parenchyma are singularly free from any invasion of fibrous tissue. The cells, for the most part, except their pigment content, seem very nearly normal. The protoplasm shows no other evidence of degeneration and the nuclei, as a rule, stain well, though here and there may be seen a very faintly staining one or one undergoing karyorrhexis.

The connective tissue trabeculæ would be prominent of themselves and are rendered much more so by the abundance of the pigment lying free between the bundles and contained also in cells. The pigment here is concentrated into narrower space and occurs in larger granules and globules.

The formation of new bile-ducts is certainly not a striking feature of the liver, but wherever found the lining epithelium contains a share of the pigment usually in fine yellow grains.

Section through the atrophied portion near the gall-bladder shows a few strands and groups of pigmented liver cells embedded in rather dense connective tissue, which is infiltrated also with small, round cells. Occasionally, there occur larger islands of liver tissue, resembling in every respect that found in other parts of the organ. In the very fibrous connective tissue surrounding the large vessels and bile-ducts in this region, there are evenly and rather sparsely scattered connective tissue cells loaded with pigment in very fine, even grains and of a slightly darker brown color than that of the prevailing type elsewhere. This

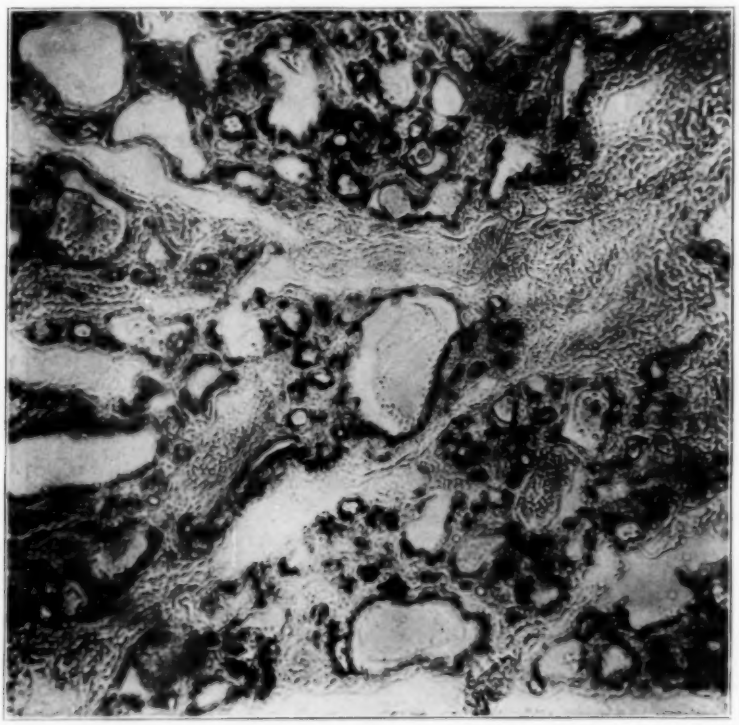

Fig. 10.—Thyroid (Case 3). Low power. Stained by Nishimura's method. Iron-containing pigment appears black in the figure and is situated in the lining cells of the alveoli.

variety (hemofuscin) is found in the adventitial cells of vessels in other sections, and has not reacted positively in any test for iron which I have used. The pigment of the liver cells, bile-ducts, connective tissue, generally, with the single exception noted, gives a positive reaction for iron.

In comparing sections treated by Perl's or Nishimura's methods the difference in distribution of the pigment in Case 1 and in Case 2 is well shown. As noted in the description of that case, the pigment in the former is present in striking amount in the liver cells in the periphery of the lobule or cell mass while those in

the center are comparatively little affected, as are also the connective tissue septa. In Case 2, the connective tissue contains the pigment in most conspicuous amounts, while that in the liver lobules is very evenly distributed.

Pancreas.—On an average about one-third of the sectional area is occupied by pancreatic tissue, the remainder of the space being filled with fat. The parenchyma is grouped together, usually, in one end of the section in lobules or islands which are separated from each other by fatty septa of varying widths. The glandular tissue itself is further subdivided into numerous small collections of acini by fibrous tissue strands which are very rich in pigment-bearing cells, a fact which renders the false lobulation especially distinct. There are in places fine strands of connective tissue between the individual acini, but this is not striking. The acini, as a rule, are poorly formed and irregular but the cells stain fairly well. Almost all the cells are pigmented with yellowish-brown granules, varying in extent from a few granules to a mass of globules. The connective tissue strands are rich in pigment occurring to some extent free in the interstitial spaces and to much greater extent contained in heavily loaded mononuclear cells. These cells are massed here and there in clumps between

Fig. 11.—Adrenal (Case 3). Low power. Hematoxylin and eosin. Figure shows capsule, heavily pigmented glomerular layer, and part of the fasciculate layer, in which may be seen a few clumps of pigment.

the groups of persisting acini and the fibrous bands, lying in small groups in the meshes of a coarse connective tissue reticulum.

In certain small, rather sharply circumscribed areas, the pancreatic cells, while still arranged in acini, have lost their usual appearance and staining reactions. The protoplasm appears swollen, vacuolated and foamy, staining hardly at all. The nucleus does not depart greatly from the usual type, but occasionally is smaller and darker. These cells, as a rule, contain a great many pigment granules gathered especially about the nucleus, but they are not by any means always the most heavily pigmented cells (Fig. 3).

The lining cells of many of the ducts contain the pigment, even those of large size. In the walls of the vessels, too, are occasional pigment-bearing cells.

The islands of Langerhans appear in all sections, but vary greatly in number and somewhat in appearance. In the head of the organ, they are quite numerous

and appear as sharply circumscribed areas of the usual size containing rather small cells in thick columns arranged in a single, simple or branching coil. Only a very few of these cells are pigmented. In the body the islands are less numerous but of typical appearance in every way and having a somewhat more complex arrangement than in the head. Here the pigmentation is more noticeable, most of the islands containing at least one or two pigmented cells. The tail of the organ is greatly scarred. There is loss of all appearance of acini; the cells are arranged in rows and small masses surrounded by strands of fibrous tissue. Hence the differentiation of the islands from the rest of the parenchyma is not so easily accomplished. Almost all of the cell areas might be taken for atypical islands of Langerhans, but scattered fairly frequently throughout the section are typical appearing circumscribed strands of cells which closely resemble those seen in other portions of the organ and like them are distinctly less pigmented than the surrounding parenchyma.

By using Nishimura's method with tissues fixed in methyl-alcohol, practically all the pigment gives an iron reaction, becoming either of a pure Berlin blue color or a dirty, yellowish-green, with many intermediate stages. Even in the best preparations, however, a little of the pigment retains its original golden character. This iron-reacting pigment does not seem to have any special predilection for any particular cell or situation, but is found now in the ducts, now in the acini, or again in the connective tissue cells. By using Perl's method, the modification recommended by Dr. Maud Abbott,[5] a greater amount of the pigment remains unchanged, more is of the yellowish-green hue and there is less showing the clear blue. In these sections, the islands of Langerhans are rendered conspicuous by the absence of the blue color and its presence in abundance in the surrounding tissues.

Spleen.—The connective tissue is diffusely increased.

The interstitial pulp is greatly decreased in amount. The Malpighian bodies are small and circumscribed. The golden-brown pigment is noticeably increased in all of the sections, but does not begin to compare in amount with that in the liver, pancreas, and other organs. Most of it is deposited, finely divided, in the walls of the sinuses with here and there larger intracellular masses. Occasionally granules and small globules are found in the venous spaces, either free or in large phagocytic cells. Many of the fine grains in the walls of the sinuses seem to be contained within the endothelial lining cells. None is found in the Malpighian bodies. The pigment reacts readily to iron tests.

Lung.—The sections show a moderate grade of emphysema. There is a moderate amount of black coal pigment. In addition to this there may be seen also yellowish-brown pigment in very much less amount, but easily distinguished from it. As a rule the hemosiderin occurs in small masses (10 or more millimeters), far apart, in the alveolar walls, either loose in the interstices of the tissues or contained in large mononuclear cells. It may be seen, also, forming small casts of the capillaries for a short distance. The small lymph-nodes within the lung substance, while containing an abundance of coal pigment, show no hemosiderin. The bronchi are slightly dilated within the lung substance and the cells of their lining membrane are definitely, though slightly, pigmented with golden-brown grains lying, usually, deeply placed in the cell, away from the lumen and in close proximity to the nucleus. The cells lining the pleura are not pigmented.

The mucosa of the higher air passages (the larger bronchi, trachea and larynx) is quite free from the pigment, which here occurs in the acini, ducts and interstitial tissue of the serous glands beneath the mucosa and in the cells of the cartilages. In the glands, the pigment is moderate in amount and finely divided into yellowish grains. Often only a few of the cells of each acinus may show the pigment; occasionally the lumen of an acinus or a duct may show a mass of the fine granules. There are mononuclear cells loaded with pigment in the interstitial tissue between the acini and in some of the glands there appears

5. Abbott, Maud: Pigmentation of Cirrhosis of the Liver in a Case of Hemochromatosis, Jour. Path. and Bacteriol., 1901, vii, 55.

to be an increased round-celled infiltration. The mucosa of the ducts shows pigmentation up to within a short distance of the lining membrane of the air passage. The cells of the cartilages, many of them, are large and well staining; many others are small and shrunken away from the matrix. Cells of both orders may contain finely divided pigment granules clustered about the nucleus or filling the whole cell. Perhaps a third or a half of the cartilage cells are thus pigmented. In the small peritracheal lymph-nodes the dilated sinuses are filled with mononuclear leukocytes which, in turn, are loaded with brownish pigment. There is no increase in fibrous tissue. The pigment in the serous glands reacts poorly to iron tests; some of it becomes blue, most of it a dirty greenish color, but never does all the pigment in a single section react positively. This is true to even greater extent of that in the cartilage cells. Most of this remains unaffected, even when treated by Nishimura's method, but the granules in some of the cells become dark green and in a very few the bluish color appears. However, that in the sinuses of the adjacent lymp-nodes reacts promptly. In these nodes the iron pigment is the only one present. There is no coal pigment.

Kidney.—There is no increase in connective tissue. The capsule of Bowman contains a granular detritus. The cells of the convoluted tubules are cloudy, swollen and much vacuolated, especially toward the basement membranes. Their lumina are irregular in shape and contain the characteristic "foamy" material of epithelial degeneration.

The pigment in the kidney is sharply limited to a certain class of tubules, having low, regular, slightly cloudy epithelium and a relatively wide empty lumen, apparently connecting or collecting tubules. The pigmented tubules are situated, principally, in the outer half of the cortex in the convoluted areas, between the medullary rays of Ferrein, though occasionally, they are found within the rays themselves. The cells often carry an excessive load of the pigment, while the immediately adjacent tubules are entirely free. The pigment reacts quite readily with the usual iron reagents. In the basal portion of the medullary pyramids, there are many tubules whose cells are much swollen and quite clear and translucent, the nucleus staining fairly well. These cells contain a few large grains of yellow pigment which does not give the iron reaction.

Thyroid.—The vesicles are normal in size and contain the usual amount of colloid. The interstitial connective tissue is not increased. Pigmentation is slight. Many of the cells lining the vesicle contain fine golden-brown pigment granules; some of them are distended with pigment, most of the cells contain little or none. On the whole, the pigmentation of the thyroid is not striking. The interstitial thyroid cells occurring in nests and strands (undifferentiated, embryonic cells?) are the most heavily affected. The pigment reacts readily for iron. There are also fine yellow grains in the coats of some of the smaller arteries.

The *parathyroids* show excessive pigmentation within the essential cells and this is rendered all the more striking by the close anatomical relationships existing between the cells. Each cell seems to contain great numbers of fine yellowish granules but with the oil immersion lens unpigmented cells can be distinguished scattered here and there. Cells with clear protoplasm are more numerous than those staining with eosin and these clear cells are the most heavily pigmented. Many of the nuclei are pyknotic and have irregular serrated edges. In the connective tissue along the larger blood-vessels are seen pigmented spindle-shaped cells. There are no masses of pigment in the interstitial tissue, which, moreover, is very inconspicuous. The pigment is iron containing (Fig. 4).

Skin.—In the basal cells of the Malpighian layer of the epidermis there is a finely granular yellowish or greenish-brown pigment in a section stained by Perl's method. There are only a few pigment grains in the underlying connective tissue of the corium.

Testes.—The epithelium of the tubules is retracted away from the capsule. Many mitotic figures occur but no spermatozoa. The tubules are far apart, the

interstitial tissue is quite loosely arranged and seems edematous. The interstitial cells of Leydig are large and prominent by reason of an excess of diffuse brownish pigment throughout their protoplasm. In the walls of many of the blood-vessels, and especially of their lining endothelium, there is a golden-brown pigment of different morphology, occurring in grains and small masses as seen in the other organs. This latter pigment reacts quite readily for iron, but that in the interstitial cells is always negative.

Bone Marrow.—The marrow of the femur appears slightly edematous. There is a peculiar fibrin-like stroma between the fat spaces. Fat greatly preponderates over the cellular elements, which are grouped in small islands throughout the sections and are present in about the normal relative proportions. There is no special alteration in the marrow, except a slight increase in the amount of pigment, most of which lies free in the spaces between the marrow cells. Much of this pigment reacts positively for iron (Fig. 5).

Adrenal.—The cells of the glomerular layer are heavily pigmented with small golden-brown granules quite regular in size and appearance. As a rule the pigmentation is sharply limited to the cells of this layer, but here and there it may be seen dipping down into the fasciculate layer to a distance of from ten to fifteen cells. Many of the cells are degenerating and some have already disintegrated, their pigment being deposited in small masses. What is evidently the track, along which this pigment is removed, may be traced up through the capsule where small granules and masses of pigment may be found in rows in the interstitial spaces or occasionally in a mononuclear cell. Even in the surrounding fat little rows of pigment resembling tiny strings of beads may be seen in the spaces between the fat cells.

The zona fasciculata is composed of quite normal-looking cells, which, however, contain less than the usual amount of lipoid material. The cells of the zona reticulata contain the usual diffuse brownish pigment in increased amounts. This is darker than the chromaffin substance of the medulla and is found in sections regardless of the method of fixation. With high powers it is slightly granular with granules very much smaller than those of the iron pigment. It is not affected in the least by the reagents used in the demonstration of iron.

In tissue fixed in formaldehyd solution and potassium chromate the yellow chromaffin substance of the medulla is found in normal, or slightly increased amounts. It occurs in similar proportions also in the cells of two sympathetic ganglia examined. In addition, there is found in the medulla another pigment occurring sparsely scattered in the medulla cells and interstitial tissue, in tissues fixed in alcohol or otherwise, and morphologically resembling the pigment found in the glomerular layer.

In sections stained by Nishimura's method, the glomerular pigment becomes blue readily. The outer third of the cortex takes a diffuse light bluish stain, which under high powers is seen to be especially localized in the spaces between the cell columns. The medulla, too, takes a diffuse light-blue stain, marking it off sharply from the reticulate zone. The pigment in the medulla, however, though resembling closely the glomerular pigment morphologically, for the most part remains unaffected by this test, only a few clusters of the granules taking on a dirty, dark green color.

Heart Muscle.—The muscle cells are moderately increased in size. The pigmentation is striking. The pigment occurs not only in the undifferentiated sarcoplasm at the nuclear poles, but also throughout the entire muscle cell in fine yellowish-brown granules arranged in longitudinal rows between the fibril bundles. The picture reminds one strikingly of that seen in a section of a fatty heart muscle stained with Sudan III. The cross striations of the muscle cells are easily seen, except where obscured by closely packed masses of pigment. The nuclei, as a rule, stain rather faintly. In cross section of the muscle cells, the pigment granules are seen to be more numerous in the center, diminishing in numbers toward the periphery in inverse arrangement to that of the fibril

bundles. Here and there, especially in sections stained for iron, may be seen a mass of granules, perhaps with a clear space in the center, and surrounded by a narrow zone of the muscle cell showing the characteristic fibril bundles. Other cells with large amounts of pigment in the center may show many small clear vacuoles in their periphery. Pigment is also found in the interstitial tissue, usually, in mononuclear cells but occasionally free. Where this pigment is greatest in amount, the fibrous tissue is increased and many small areas of fibrosis may be found containing heavily pigmented mononuclears and one or two pigmented and atrophying muscle cells. In sections stained by Nishimura's method all the pigment takes on a beautiful blue color. No unaffected granules can be found, even immediately at the nuclear poles after careful search. Perl's method leaves some unchanged pigment at the nuclear poles.

Gastro-Intestinal Tract.—The mucosa and submucosa of the stomach are slightly edematous. The glands at the base of the mucosa are deeply pigmented. The pigmentation becomes less toward the surface and none is found in the superficial half of the mucosa. An occasional pigmented mononuclear cell is found in the interstitial tissue. There is no pigmentation of the muscle.

Sections of the small intestine show marked edema, especially of the mucosa and submucosa. There is no pigmentation.

Lymph-Nodes.—Sections of all lymph-nodes examined, with the exception of the bronchial, contain a larger or smaller amount of iron pigment, both intracellular and free in the interstitial tissue. There is also in many cases a chronic lymphadenitis with marked increase in fibrous tissue. Where the pigmentation is slight, it is found especially in the periphery of the sinuses along the lymph-nodes and cords, but in more extreme cases may be found in dense masses in the nodes and cords.

CASE 3.—*Medical No. 24,059. Hemochromatosis with Diabetes Mellitus. Onset with Diabetic Symptoms Five Months Before Death.*

R. D., white, farmer, 44 years old, was admitted to the Johns Hopkins Hospital May 20, and died June 5, 1909.

Complaint.—General weakness.

Family History.—Excellent. The patient has been married twenty-three years. His wife is in excellent health. There are three children.

Past History.—In general the patient has been a hearty man and enjoyed excellent health. He had the usual diseases of childhood.

Lesions of the head, cardial, respiratory, neuro-muscular and genito-urinary systems were carefully inquired for with negative results.

Gastro-Intestinal.—He has always been a hearty eater, thinks he often ate too much, but suffered very little from indigestion. He occasionally had indefinite pains after eating. Bowels have been constipated since the present illness began, but before this for fifteen years were loose with two or three passages each day. Twelve years ago he had dysentery which lasted for one year. It was characterized by bloody, mucous stools and great abdominal tenderness. He was never jaundiced and has not noticed the presence of hemorrhoids.

Habits.—He is a hard worker and has undergone considerable exposure. Formerly he was a heavy smoker, but has used no tobacco since last fall. He has never been addicted to alcohol. Since the onset of the present illness he has taken a little whiskey twice a day. Before that he drank very little whiskey and no beer.

His average weight is 175 pounds. He has lost 40 pounds.

Present Illness.—This began about six months ago with an attack of indigestion for which his physician advised drinking of quantities of water. Following this advice the patient gradually developed a marked polydipsia and polyuria with the urine of pale color. He noticed that he ate more than formerly, but nevertheless lost weight rapidly. His bowels became constipated until a cathartic was always required. The patient grew weaker and weaker, finally becoming

exhausted after the slightest effort. In February, three months ago, he spoke to a physician, who on examination found sugar in his urine. Sexual power is much diminished.

Physical Examination.—The patient is a large man, has evidently lost weight. The pigmentation over the dorsum of the hands, over the face and neck, and over the legs and feet, from the knees down, is of an extreme brown color. The nipples, axillæ, genitalia, and skin of the body show no increase. There is scattered freckling over the chest and arms. The skin is dry and scaly. There is very little beard and the hair elsewhere is small in amount.

The pupils are unequal and react to light and accommodation.

The tongue is cracked and coated; the throat injected; and there is pus in the posterior pharynx. There is no general glandular enlargement.

The heart and lungs are negative.

The spleen is not felt.

The liver is enlarged, the dulness beginning on the fourth rib, flatness on the sixth rib and extending to the costal margin. The edge is felt at a point 3.5 cm. below the costal margin in the right mammillary line, is smooth, firm and resistant. It crosses the midline 7.5 cm. below the ensiform.

Descent of the liver with respiration is visible. There is also seen some lazy peristalsis about the umbilicus. Just to the right of the umbilicus there is a tender prominence corresponding to the head of the pancreas. No definite mass can be felt.

Genitalia.—The right testicle is atrophied.

Extremities.—There are no scars nor edema. The deep reflexes are sluggish. The left knee jerk is obtained on reinforcement; the right knee-jerk not at all, nor are any of the other deep reflexes.

Urine on admission was pale yellow, acid, of specific gravity 1,030 and contained 48.6 gm. of sugar in the twenty-four-hour specimen, or 5.4 per cent. There was no albumin nor any casts. Acetone and diacetic acid were present. For subsequent examinations see the table.

Examination of the Blood.—Red cells, 5,320,000. Leukocytes, 7,080. Hemoglobin, 94 per cent. (Sahli). In a preparation of the fresh blood the red cells seem normal in size, shape and color. The blood smears readily with tendency to rouleaux formation. There are no evidences of degeneration. The leukocytes are not increased; no eosinophils are seen. Numerous fat droplets are seen in fresh smears. The diagnosis is verified by staining with Sudan III.

On June 3, the temperature, which had been about normal, rose to 100.2, and a red, tense, boggy swelling was discovered in the region of the left parotid gland. For the past few days the patient had been growing weaker and more toxic with a marked, fruity odor to the breath. The skin was very dry and desquamating on the hands where the pigmentation was definitely increased.

Over the abdomen there were many small reddish-purple spots, the color of which did not fade on pressure.

The liver seemed slightly larger than before and somewhat tender.

Blood Examination, June 4.—In a fresh smear the red cells show moderate distortion with tendency to a raquette shape. The color appears normal. No fat droplets are seen. Leukocytes number 3,000 per c.mm.

Later the right parotid became swollen and tender and the coma deepened in spite of increased carbohydrate in the food and intravenous infusions of alkali.

On June 1 the Wassermann reaction of the blood serum was negative.

The temperature remained about normal until June 2, when coincident with the parotid infection, it rose to 100.2. It continued to rise gradually until on the evening of June 4 it was 107, and the pulse 130. Just after the death of the patient some blood was aspirated from the right auricle. This showed great numbers of *Staphylococcus aureus* in pure culture.

Clinical diagnosis: Hemochromatosis; diabetes; double parotitis; septicemia.

Autopsy No. 3,228. (Autopsy one hour after death.)

Anatomical Diagnosis: Hemochromatosis (bronze diabetes); extreme pigmentation of liver, pancreas, lymph-nodes, heart, gastric mucosa, thyroid, submaxillary gland, Brunner's glands, adrenals, parathyroids, prostate, testes, seminal vesicles, and skin of face, hands, and lower legs; cirrhosis of liver, pancreas and lymph nodes; chronic splenic tumor; ascites; purulent tonsillitis; acute diphtheritic enteritis; edema and atelectasis of lungs; chronic adhesive pericarditis; chronic gastritis; chronic orchitis with atrophy; chronic fibrous myocarditis; chronic prostatitis.

TABLE 2.—URINARY FINDINGS, CASE 3

Date.	Total Amount of Urine in c.c.	Specific Gravity.	—Sugar— Per Cent.	Gm.	Acetone.	Diacetic Acid.	Diet.
5/21	900	1.030	5.4	48.6	+	+	Ward diet.
5/22	2,930	1.032	4.4	129.	+	+	Ward diet.
5/23	2,600	1.033	6.	156.	+	+	Ward diet.
5/24	2,230	1.035	5.	113.	+	+	Carbohydrate-free, plus white bread, G. 25
5/25	2,300	1.035	2.5	32.	+	+	Carbohydrate-free, plus white bread, G. 25
5/26	2,920	1.035	2.3	67.	+	+	Carbohydrate-free, plus white bread G. 25
5/27	3,850	1.035	1.	38.	+	+	Carbohydrate-free, plus white bread G. 25
5/28	2,600	1.025	1.1	28.	+	+	Carbohydrate-free, plus white bread G. 25
5/29	2,600	1.025	0.5	13.	+	+	Patient refuses bread.
5/30	2,530	1.022	0.5	11.6	+	+	Patient refuses bread.
5/31	1,610	1.025	0.7	11.2	+	+	Patient refuses bread.
6/ 1	1,300	1.025	*	....	+	+	Glucose G. 10, q. h. ad. G. 50
6/ 2	1,750	1.021	1.5	27.	+	+	Glucose G. 10, p. h. ad. G. 50
6/ 3	2,680	1.025	3.9	104.	+	+	Glucose G. 10, q. h. ad G. 50
6/ 4	2,710	1.025	3.7	97.	+	+	.....
6/ 5	....	....	..	....	..	..	.....

*Levorotatory.

The body is that of a large, fairly well-nourished, white man, 175 cm. long. The face and hands are deeply "sun-burned." The lower legs show a definite pigmentation, but not nearly as marked as the hands. The skin over the arms, legs and thorax is dry and scaly. The hair is slight in amount over the pubis and absent over the chest. There is a very small amount of subcutaneous fat. The abdominal cavity contains 1.5 liters of a clear, lemon-yellow fluid.

The *heart* is cut and torn considerably on removal through an abdominal incision. The pericardium is loosely adherent by old fibrous adhesions. The cavity is completely obliterated. The heart is small and the right side dilated. The left auricle is slightly dilated but not thickened, while the left ventricle is tightly contracted. The wall of the left ventricle measures 12 to 14 mm. The valve segments are all quite delicate with the exception of the aortic valves which though slightly thickened were evidently competent. The tricuspid ring measures 12 cm.; the mitral 9.5 cm. The myocardium of the right ventricle is a bright yellowish-brown color. Tangential section of the muscular wall of the left ventricle shows a very diffuse translucent tissue replacing a good deal of the heart muscle which is of a deep bronze color. The root of the aorta shows a considerable amount of sclerosis, especially around the orifices of the coronary arteries. The coronary arteries are diffusely thickened.

The *lungs* were edematous and showed some hypostatic congestion.

The *spleen* weighs 250 gm. and measures 13 by 8 by 4.5 cm. The capsule is thick, irregular and granular. On section the organ is of a uniform, dull red

color. The trabeculæ are prominent, while the Malpighian bodies are very small and hard to see. The pulp is elastic and does not scrape off on the knife.

The *stomach* is dilated with fluid and gas. Its mucosa has a definite, rusty, pinkish color. On section this is seen to be due to a pigmentation of the mucosa. The muscle coats appear pale and normal. The rugæ are considerably obliterated and the mucosa has a stamped leather appearance.

The *pylorus*, *duodenum*, and *bile-ducts* are normal.

The *gall-bladder* contains a very thick, slimy, black bile.

The *pancreas* is of a deep bronze color. It is definitely enlarged and somewhat increased in consistence. On section the lobules seem glued together.

The *liver* weighs 3,200 gm. The surface is slightly irregular and the edges rounded. The organ is very tough and elastic, and is deep bronze-red in color. Section is quite uniform in appearance, and has a rough, granular appearance. The lobules are greatly distorted; some of them being larger than normal. There are numerous depressed scars all over the cut surface. The vessels stand wide open. The liver tissue everywhere has this deep bronze tint. The connective tissue in some places is slightly translucent and grayish looking.

The right *kidney* measures 11.5 by 5.5 by 4 cm. and weighs 200 gm. Both kidneys show some congestion and cloudy smelling.

The *adrenals* are of normal size and general appearance except for a slight increase in pigmentation. The cortex is 2 mm. in thickness and the striæ yellowish brown. The inner zone is deep brown, while the medulla is inconspicuous.

The *lymph-nodes* about the head of the pancreas, at the hila of the liver and kidneys and along the aorta are greatly enlarged, some of them measuring 2 or 3 cm. in long diameter. They are firm, but not very tough; in some instances indeed rather soft. They are deeply pigmented, the color showing distinctly through the capsule. On section this pigment is found to be of bright yellow or deep brown color. Some of the nodes below the thyroid are enlarged and show a definite rusty pigment, as well as black coal pigment. Their bronze tint, however, is not so marked as that of the nodes about the liver. Those just above the bifurcation of the trachea measure from 1.5 to 2 cm. in diameter, and are of a uniform, deep, rusty-brown color. They are conspicuous also just above the base of the heart. Here the pigmentation is as deep in some instances as the nodes in the neighborhood of the liver. Other nodes are scattered all through the fat of the anterior and posterior mediastinal regions. Many of them are of the size of small peas, and all are more or less pigmented. The nodes posterior to the hilum of the lung form a rather conspicuous chain along the esophagus. These, too, show a deep yellowish-brown, uniform pigmentation with a rather conspicuous amount of connective tissue. They are of all sizes and in places somewhat matted together. The bronchial nodes are enlarged and more or less pigmented, but contain more black than yellow pigment. The nodes become more conspicuous as we go along the aorta downwards, and their architecture is very sharply marked out by the bright yellow pigment. They are very numerous and large along the lumbar region, where they form a continuous chain beside the aorta. The nodes in the pelvis do not show this pigmentation, but are of a uniform, pinkish-gray color. They are somewhat larger than normal and rather juicy. The mesenteric nodes are examined with considerable care. They are slightly increased in size, some of them measuring 1 or 1.5 cm. in long diameter. They are uniform, pinkish-gray and on section moist and juicy, but have no abnormal pigmentation. They contrast very conspicuously with the nodes around the duodenum and pancreas close beside them which contain large amounts of the ochre pigment, together with a certain amount of black pigment in some instances.

The *aorta* shows a moderate grade of sclerosis throughout its entire course.

The *submaxillary gland* has a regular architecture. The gland acini are pigmented a deep yellowish-brown, much the color of maple sugar.

The left *tonsil* is large, hemorrhagic in appearance and contains some pockets of creamy material. *Pharynx*, *larynx* and *esophagus* are quite normal.

The *thyroid* is rather small and fibrous, and on section the connective tissue is rather conspicuous. The colloid substance is easily seen. The tissue has a deep bronze tint.

The *parathyroids* are of normal size and appearance, but the pigmentation is darker than that of the normal gland.

The *jejunum* is considerably dilated, and its mucosa swollen, pink and velvety-looking. No ulcerations are present. The same condition is found in the upper part of the *ileum*, but 60 cm. from the ileocecal valve the mucosa becomes very deep red, swollen and edematous and in places has a charred, granular appearance. The surface is covered with little knobs and tags of granular fibrin. The surface throughout is granular and dry. The same condition is found in the *cecum*. There are thickly scattered ecchymotic patches. In the *sigmoid* a considerable membrane of rather uniform appearance is found.

The *bone-marrow* of the femur is somewhat cellular, but soft and flabby. About two-thirds of the tissue is evidently fat, the remaining third being pale and cellular.

The right *testicle* is very small, most of the gland tissue being replaced by radiating scars. The tubules, where remaining, have a very pale, brown color. The left testicle, in general, has the same appearance, but is larger, measuring about 2 cm. in long diameter. There are scars in this testicle as well. The tubular structure has a deeper brown color.

MICROSCOPIC EXAMINATION

Liver.—The liver is divided into lobules, varying greatly in size and shape, by rather broad and cellular bands of fibrous tissue.

The pigmentation is very heavy, more marked than in the other cases, and very evenly distributed throughout the section. Each cell is almost filled with the mass of very fine brown granules. The nuclei are often eccentric and rather small. In every lobule there are one or more areas in which the cells are broken down and the pigment lies free in heavy masses or contained in phagocytic cells. These areas resemble those already fully described in the preceding cases. There are other places in which the cell relations are preserved but the cells excessively vacuolated and poorly stained in addition to being heavily pigmented. A prominent feature of this liver is the presence of nodes of liver cells, larger than their fellows, with large deeper staining nuclei and containing very little or no pigment. They vary from 0.25 to 0.5 mm. in diameter, are round or oval and are evidently masses of newly formed liver cells. In the recently regenerated areas the cells of Kupfer are heavily pigmented as elsewhere in the sections, while the parenchymatous cells contain only a fine, dust-like pigmentation, and occasionally even this is not evident (Fig. 6). There are other more or less circumscribed areas in which the cells are more definitely pigmented, but much less so than in most of the surrounding tissue, representing probably regenerated tissue of longer standing.

The connective tissue septa are rather cellular and contain numerous fine capillaries. Pseudo-bile-ducts are fairly numerous, also, and always pigmented. Pigment is found scattered throughout the connective tissue in the interstitial spaces, in wandering cells, in the pseudo-bile-ducts, and in the endothelium and walls of blood-vessels, but is less abundant, compared with that of the liver cells, than in the other cases of this series.

The so-called pseudo-bile-ducts are among the most heavily pigmented structures found. Transitions may readily be traced from the ordinarily pigmented liver cell, through those more heavily pigmented which are arranged in two parallel rows and the very heavily pigmented pseudo-bile-ducts, to those in which many of the cells have been entirely destroyed leaving an elongated mass of free pigment. Many such elongated structures are seen, one end consisting of heavily pigmented cells and the other of free pigment masses.

The connective tissue tends to be annular in arrangement, and does not invade the masses of liver cells to any extent. The lobulation is quite evidently a false

one. Sometimes a central vein may be located near the periphery of a mass of cells. Often the most degenerated areas and the newly regenerated portions seem to be in close relation to a central vein, and occasionally, a new growth of pigmented connective tissue can be found about what is apparently a small radicle of the hepatic vein. The endothelial cells of the blood-vessels, large and small, are frequently loaded with pigment, but the true bile-ducts contain little, and often are entirely free.

Hemofuscin is present in considerable amount in the walls of blood-vessels. Elsewhere the pigment reacts positively in iron tests.

Pancreas.—Sections of pancreas show a distinct lobulation, and there is practically no infiltration of fat between the lobules. The gland is heavily but not uniformly pigmented. Every cell seems to contain at least a few grains and the majority are but slightly pigmented, but there are several patches in each lobule in which the cells are loaded with pigment or have already disintegrated with the deposit of masses of pigment and the ingrowth of granulation tissue. These areas resemble those in the liver, but the focal nature of the pigmentary degeneration is much more pronounced in the pancreas.

In the least affected regions, the acinar arrangement, while not so clear and distinct as normal, is quite evident. The cells are slightly or moderately pigmented, their nuclei stain well, in some cells pyknotic, but the borders of the cells are very indistinct and they fade into each other. Some sections show edema where the acini are forced apart and rendered more distinct. In others they are close together and at times resemble cords or masses of nuclei with little distinct acinar arrangement. There is only the slightest amount of connective tissue growth in these less affected zones.

On the other extreme there are found masses of pigment, which, on close examination, reveal themselves to be excessively pigmented cells sometimes barely preserving some trace of their former arrangment. Into such areas, the connective tissue is growing and the later stage of deeply pigmented scar tissue may also be seen.

There are intermediate stages, also, in which heavily pigmented cells preserve their glandular arrangement.

The interlobular connective tissue is slightly increased in amount and shows scattered pigmented wandering cells. The mucosa of the larger ducts is free from pigment, but their walls and those of the blood-vessels show pigment bearing cells.

All the islands of Langerhans are either in the center of or in close association with one of the areas of excessive pigmentation and degeneration (Fig. 7). The islands vary in size; some few are large and well formed, more are quite small and contain only a few cells which are, however, well preserved. They are not numerous, however, and the degenerated areas are seen frequently without an island of Langerhans. As a rule, each island contains a few pigment granules.

The pigment reacts positively to tests for iron, except that in the walls of the large blood-vessels. This pigment is very finely divided and of a lighter color (Fig. 8).

Heart Muscle.—The heart muscle is deeply pigmented and here, too, the pigmentation is patchy. There are groups of cells heavily loaded throughout their protoplasm with the golden-brown grains alternating with other areas, in which the pigmentation is much lighter and more nearly confined to the undifferentiated sarcoplasm at the nuclear poles. The pigmentation is heavier than in the preceding case, but there has been little destruction of cells. A few very small areas may be found, in which occur mononuclear wandering cells loaded with pigment, but for the most part the pigment is confined to the intact muscle cells. The nuclei, as a rule, stain well; in some cells, the chromatin is small in amount. The appearance of the individual cells conforms to the description given for the preceding case. Almost all the pigment reacts positively to iron tests. It is only by rather careful search that some unchanged pigment is seen (Fig. 9).

Spleen.—There is a diffuse increase in the connective tissue. Many large pyknotic and karyorrhetic nuclei are seen, the protoplasm of their cells staining deeply with eosin. There is a slight increase in pigmentation. The pigment is found in golden-brown granules or small masses, scattered here and there throughout the splenic pulp. It is found, usually, in phagocytic cells with very irregular vesicular nuclei and often occurs free in the interstitial tissues or in the sinuses. Occasionally, heavily loaded phagocytes show marked signs of degeneration with nucleus undergoing karyorrhexis or karyolysis, but the majority of the large pink cells with pyknotic nuclei are free from pigment. No pigment is found in the large lymphocytes nor in the endothelial cells lining the sinuses. The pigment reacts positively to iron tests.

Submaxillary Gland.—There is a definite increase in the amount of connective tissue which is principally interlobular in distribution and to a less extent interacinar. In structure, it is loose and cellular with many mononuclear cells in its interstices.

The parenchymatous cells are practically all pigmented with finely divided golden-brown granules. Some of the tubules are heavily loaded, their structure almost lost or obscured by the surrounding granulation tissue; others are only slightly affected with a few scattered grains. Serous tubules greatly predominate, but there occur, scattered through the gland, groups of tubules which have a very well-defined basement membrane and practically clear non-staining cells with small, dark misshapen nuclei lying close to the basement membrane. A very fine, delicate network can be made out in some of the cell bodies and fine lines marking the cell boundaries. Most of these cells show scattered pigment in fine grains. There are crescent-shaped serous cells around the ends of these tubules—the demilunes of Giannuzzi—which, like the other serous glands, are much more heavily pigmented. Usually the demilunes are distended with the golden-brown granules and stand out very prominently in contrast with the clear mucous cell-bodies. In some of the mucous tubules the cells cannot be distinguished or nuclei found. There is simply a foamy, almost clear, space surrounded by the crescents and basement membrane. The serous tubules are the more heavily pigmented. Many of them are filled with granules, while others are only slightly affected. In most cases, the tubular arrangement is well preserved, but in places this is quite indistinguishable, and the cells are found apparently in columns and strands.

The connective tissue is almost free from pigment. A few pigment-bearing cells are found on careful examination. Some of the small interlobular arterioles have in their walls a pigment which very closely resembles that of the gland cells, but is perhaps of a lighter color. This pigment does not give a positive reaction with Nishimura's method, while the great majority of that in the secreting cells does. There is some brownish pigment remaining unaffected by the ammonium sulphid and other reagents. It is scattered rather diffusely throughout the sections and seems to belong especially to the serous glands. Unlike most reported observations, the pigment of the demilunes of Giannuzzi reacts positively as a rule, though in a few places there was no change in color. I could determine no difference in the cells or pigment which showed positive tests from those reacting negatively. Sometimes the same cell contains both blue and brown granules. The protoplasm of the mucous cell stains a diffuse light blue by Nishimura's method while their pigment grains stand out as much darker blue.

Stomach.—The section of tissue preserved shows both stomach and duodenum with the usual gastric glands and at the other end of the section typical Brünner's glands. The secretory cells are heavily pigmented with a very finely and evenly divided golden-brown pigment. This pigmentation involves those glands near the muscularis mucosæ especially and extends to a point about half-way to the free surface of the mucosa.

There is no pigment in the superficial half of the mucosa. All the cells of Brünner's glands are also heavily pigmented and the cells of their ducts contain granules to a point about half way through the mucosa. Some of the cells have

excessive deposits and show poor staining and distortion of the nuclei. As a rule, however, each cell contains only a moderately heavy accumulation in the end of the cell toward the lumen of the tubule. Only rarely is there found a pigment granule in the interglandular tissue. All this pigment gives a positive reaction for iron.

There is another pigment in the section which differs from the foregoing, especially in its failure to respond to iron tests and in its characteristic location. It has, too, a somewhat different morphology, being in finer particles and having a slightly lighter color. This is found in the walls of the blood-vessels. Here and there a muscle cell of the muscularis mucosæ or of the main muscular coats may show these fine yellowish-brown grains. It is found in the vessel walls characteristically in rather blunt, spindle-shaped cells with light blue oval nuclei, but here and there the pigment seems to be in the muscle-cells themselves. Occasionally the containing cell is quite large, irregular in shape with a large round or somewhat distorted, vesicular nucleus. This pigment is absolutely unaffected, apparently, by the various reagents used microchemically to detect iron, and corresponds to von Recklinghausen's "hemofuscin." According to many writers, in sections stained with methylene blue, the hemofuscin takes a darker color, blue or violet, and is thus rendered much more distinct. I have been unable to substantiate this in this case. The pigment remained unaffected by Gruber's polychrome-methylene blue. Perhaps there is some difference in the stains used.

Sections from the duodenum lower down show a similar picture. In sections from the lower portion of the jejunum no iron reacting pigment (hemosiderin) is found and but little of the non-reacting hemofuscin in the walls of the vessels. There is, however, a striking inflammatory condition of the common type. Hemofuscin is present in the walls of the larger vessels but much less conspicuously than in the duodenum.

Lower down in the ileum the inflammatory process is further advanced and more hemorrhagic. The prominence of the acute condition overshadows any possible chronic enteritis which may have been present. The mucosa seems decidedly thin, however, and somewhat distorted. Hemofuscin is found in the vessel walls in amounts similar to that in the jejunum, and in addition, it may be quite plainly seen here and there in the fibers of the longitudinal muscle coat. Perhaps the excessive edema causes it to stand out more prominently. The pigment is not noted in the circular layer whose fibers are cut transversely.

Section of the colon shows dilatation of blood-vessels, some edema of the submucosa with the presence of large mononuclear cells in slightly increased amounts, and a few polymorphonuclear leukocytes. The mucosa and the muscle coats seem quite normal. In the interglandular spaces and very near the surface of the mucosa there is found a goodly number of large cells, mononuclear, which are distended with a very fine brownish pigment. They seem to be in close association with the capillaries. They are not observed in the depths of the mucosa, and no other pigment is seen in the section. It does not give a positive iron reaction.

Thyroid.—The cells lining the alveoli are heavily pigmented, even more so, perhaps, than those in Case 1 and much more than Case 2. The alveoli, themselves, are larger and contain more colloid material than in the first case, giving a slightly different picture, but except for the pigmentation neither gland is far from normal.

As in the first case, it is in the smaller, more irregularly shaped alveoli, containing a small amount of colloid, that the cells are most heavily loaded. This may be stated as a general rule, but is by no means invariable. The nuclei may be obscured or pushed aside, but where plainly seen are always apparently in good condition. Pigment is not found in the interstitial tissue. Instead of the usual hemofuscin, the larger darker granules of hemosiderin are present in quite noticeable amounts in spindle-shaped connective tissue cells in the walls of the blood-vessels.

The pigment in the glandular cells reacts positively to iron tests, but not so readily as that in some other situations (Fig. 10).

Kidney.—The capillaries, including those of the glomeruli, are congested and the convoluted tubules show a mild grade of parenchymatous degeneration with swollen granular cells surrounding a lumen, which contains a small amount of detritus. There is very little pigmentation. This occurs in small groups of three or four collecting tubules either in or close to the pyramids of Ferrein. Sometimes Henle's loop is involved. Those tubules which are affected at all have a heavy deposit. The pigment occurs in rather coarse grains, which not infrequently distend the cell, pushing the nucleus aside. It reacts quickly with iron reagents. No hemofuscin is found.

The amount and distribution of the pigment in the kidneys of the three cases are practically the same.

Testicles.—Section from the right testicle shows a greatly thickened capsule and complete atrophy of the seminiferous tubules. The basement membranes are intact and thickened, but only traces of cells remain in the tubules which are shrunken and massed together in lobules separated by bands of thick, fibrous tissue. The interstitial tissue between the tubules is loosely arranged and shows the presence of large mononuclear cells and thick walled, hyaline capillaries but no pigmented cells of Leydig are seen. Both the capillaries and larger vessels have greatly thickened walls, many of them showing advanced hyaline degeneration. There is a striking pigmentation of the endothelial lining cells of these vessels and of their walls, as well. The pigment is in rather coarse golden-brown grains and gives the iron reaction readily, even that part of it in the muscular walls of the vessels, the characteristic site of hemofuscin.

With Perl's and Nishimura's tests the whole vessel wall sometimes takes a diffuse light blue color, but the dark blue granules stand out quite distinctly. This pigmentation extends to the vessels of the thickened capsule and is quite prominent there. The pigment in the testis in Case 2 shows the same distribution, but in much less conspicuous amounts. In no other organ have I found such extensive pigmentation of the endothelial and muscle walls of the vessels, and in this organ and the thyroid only have I found pigment in the muscle wall of an artery reacting positively in tests for iron. No pigment whatever is seen which is not iron-reacting.

Sections from the left testicle show apparently the same process in a less advanced stage. The capsule is thick as are also the basement membranes of the tubules. The germ cells are in various stages of degeneration. Mitotic figures are seen, but no spermatozoa. Running through the section are broad bands of loosely arranged fibrous tissue containing shrunken atrophic tubules like those in the other gland. The interstitial tissue is edematous and contains mononuclear cells and capillaries similar to those in the right testis. In addition, there are also present the cells of Leydig with an excess of very fine, diffuse, yellow pigment throughout their protoplasm. This pigment is negative in all iron tests. In the tubules themselves there occurs a diffuse yellow pigment quite similar, if not identical, with that in the interstitial cells. As a rule it is found in degenerated cells with a vacuolated protoplasm often showing no nucleus, and may be seen in small or moderate amounts in all the living tubules, but rarely in those completely atrophied. It occurs occasionally in large yellow masses in the lumen of an atrophic tubule either free or within a cell, the nucleus of which is still visible. This pigment does not give the iron reaction.

The amount of the iron-reacting pigment in sections of the left testicle is very much greater than in those of the right, and there is a very distinct difference in the same section between the pigment content of those vessels in the atrophic, scarred areas and that of the vessels in the better-preserved portions. In the latter, the endothelial cells seem to be almost completely filled with pigment, while in the scars between the atrophied tubules the vascular endothelium is only moderately or slightly pigmented and occasionally not at all. This may be partially explained by the fact that the vessels in the scarred areas have

smaller lumina, thicker walls and more frequently show hyaline degeneration. But this is not sufficient, since vessels of the same size and similar appearance, otherwise, show great difference in their pigment content, dependent, apparently, in some way, on their relation to the seminiferous tubules.

Prostate.—Judging from the piece of tissue cut for microscopical examination, the prostate was about normal in size and configuration. Histologically there is a moderately advanced chronic prostatitis. The gland acini seem slightly compressed by the somewhat hypertrophied stroma.

The cells of the acini are fairly heavily pigmented with golden-brown grains which react positively in iron tests. The endothelium of the capillaries in close association with the basement membrane is frequently heavily loaded with hemosiderin which in some fields is more conspicuous than that in the epithelial cells. The prostatic ducts contain less pigment. As a rule, the nearer the urethra, the less pigment, and the greater proportion of granules which do not react positively for iron. A few cells in the lining membrane of the urethra contain clusters of hemosiderin granules about the nucleus. These are quite sparsely scattered and are found only in the deeper layers near the basement membrane.

The capillaries and small vessels of the stroma are pigmented in a way quite similar to that in the testicles, but to much less extent.

The epithelial cells of the vas deferens in the ampulla and of the seminal vesicles, both the stratified cylindrical lining membrane and the columnar and cubical cells of the glands, are heavily pigmented with a light yellow granular material which does not give the iron reaction. This same pigment is found in large quantities in the vas deferens further back and in the epididymis as well. In color it closely resembles that in the testis.

Hemosiderin is present in small amounts in the capillaries of the interstitial tissue in all sections of the sexual apparatus.

Adrenal.—The sections of this organ very closely resemble those of the preceding case. There is the same heavy pigmentation of the glomerular zone with hemosiderin (Fig. 11), the increase in the normal pigment of the reticular zone and the presence of a few pigment granules in the medulla, some reacting positively for iron, others negatively. There are, however, minor differences. In this case the pigmentation of the outer layer is more general, involves more cells and more frequently dips down into the fasciculate layer as a long continuous or interrupted strand of pigmented cells. The pigment grains are even and regular in size and are gathered around the nucleus in the less heavily affected cells. Many cells are filled with pigment, but the nucleus, as a rule, stains well and only occasionally is there evidence of cell destruction with the deposition of small masses of pigment. There is really more pigment present in this adrenal than in that of the preceding case, but one gets the impression that the process is much more recent and less complete. There is little cell destruction, little pigment has been set free in the interspaces and the lymphatics cannot be traced by their injection with pigment as in Case 2. In both cases there seems to be less of the lipoid substances in the cortex than normally. The pigment in the zona reticulata is unaffected in the iron tests.

In tissue fixed in formaldehyd solution and potassium chromate, the medullary cells show a very diffuse yellow pigment. In addition there are many granules closely resembling those of hemosiderin in size and appearance, but they are not present in tissue fixed by other methods. The chromaffin tissue of the adrenal seems to be about normal or slightly increased in amount; certainly not diminished. The sympathetic ganglia and other tissues, in which this material occurs, were not examined.

Skin.—The cylindrical basal cells of the Malpighian layer of the epidermis contain a fine yellowish-brown pigment which is not affected by ammonium sulphid or by potassium ferrocyanid and hydrochloric acid. This pigment varies in amount in different cells from that scarcely perceptible to a very considerable pigmentation.

In the corium and subcutaneous tissues there are many scattered, branched, spindle-shaped or elongated cells containing the familiar iron-reacting, golden-brown granules of hemosiderin morphologically and microchemically identical with that in the internal organs. The nuclei of these cells are round, oval or irregular and elongated with a very distinct nuclear membrane and no definite nucleolus. The cells are in general scattered evenly between the connective tissue fibers, except about the blood-vessels, where they are collected in large numbers. The endothelium of the vessels is entirely free. In the muscle coats iron-free hemofuscin granules are occasionally seen. No sweat glands are seen in the sections of tissue available.

This picture is quite different from that presented in Case 2, where the pigmentation is limited to the basal cells of the epidermis and does not react positively in iron tests. Both kinds of skin pigmentation are reported and quite naturally have led the observers to different views concerning the clinical value of a microscopic examination of the skin in a suspected case of hemochromatosis.

Bone-Marrow.—The bone-marrow of the femur shows some edema, slight hyperplasia and a small increase in pigmentation. The general appearance is like that in the preceding case. There is the same preponderance of fat and the edematous areas between the fat cells containing the fibrin-like stroma, but the blood-forming cellular areas are slightly more numerous than in Case 2. The hematopoietic islands are not uniformly scattered among the fat cells, but many are grouped in one corner of a section while there are many fields in another portion of the same section which show nothing but fat. Cells of the myelocytic series greatly predominate, but here and there are found groups of megaloblasts and normoblasts. The hyperplasia is, however, very slight and in no way suggests any active new blood formation. The pigment is rather less than in Case 2 and for the most part is intracellular and iron-reacting. The endothelial lining of the blood-vessels contains no pigment.

Lymph-Nodes.—In the bronchial nodes, hemofuscin is present in considerable amounts in the walls and adventitia of blood-vessels and in the capsules of the nodes. In one, especially, in which the hemosiderin is relatively small in amount compared with that in other nodes, and in which there is even less coal pigment, the black pigment is more nearly in the center of the lymph-cords, while the iron-containing pigment is confined to the sinuses or their immediate neighborhood.

Those from the anterior and posterior mediastinum contain a moderate supply of hemofuscin and hemosiderin along with more or less coal pigment and show the presence of more fibrous tissue. In the tissue between separate nodes there are many connective tissue cells containing hemofuscin and small strings of hemosiderin suggesting its passage through lymph-spaces and vessels.

There are sections of several mesenteric nodes which in gross were not pigmented. In one there is a rich accumulation of hemofuscin in the walls of the vessels and in the capsule and a small amount of hemosiderin in the sinuses and cords, which might be easily overlooked with low powers of the microscope. On more careful examination, it is found to be present in amounts about equal to or somewhat greater than, for example, that in the spleen. Another smaller node shows conspicuous hemofuscin in the vessel walls, but not so much in the capsule and connective tissue generally. The hemosiderin is present in very small amount, collected here and there into large, tightly packed mononuclear cells.

A pelvic node shows a great deal of hemofuscin in its capsule and vessel walls and only an occasional small granule of hemosiderin. The sinuses in one portion are widely dilated and contain a few very large mononuclear cells. There is no trace of the fine yellow pigment seen in the sexual organs.

The most heavily pigmented are the portal nodes and those immediately surrounding the splenic artery. Some of these seem to have been converted into masses of pigment which completely obscure the structure of the larger part of the node. The trabeculæ are increased in thickness, and are quite prominent. In the connective tissue cells of the capsule, trabeculæ and walls of the vessels,

hemofuscin is present in large amounts. It is especially conspicuous at the hilum of the nodes where the connective tissue trabeculæ are most prominent and the many cells are filled with the fine yellowish-brown granules which do not show microchemically the presence of iron.

The walls of the *splenic artery* are not pigmented or at most show a few granules here and there in the adventitia. The intima is not thickened nor is any abnormality observed. In the surrounding connective tissue, hemosiderin is found in the endothelium of the capillaries including those of the nerves, but neither here nor in any other sections has pigmentation of the nerve tissue itself been noted. Hemofuscin is found in the walls of the smaller vessels.

Sections of the *aorta* show a slight irregularity in the thickness of the intima which is not, however, anywhere markedly thickened. The media seems normal, and there is no pigmentation noted in any of the coats nor in those of the vasa vasorum. The cells of the peritoneum above the aorta stain deeply, but no definite granular pigmentation is observed. In the connective tissue immediately below the serous layer there are a few scattered cells containing a yellowish-brown pigment resembling hemofuscin.

MICROCHEMICAL REACTIONS OF PIGMENTS

In studying the effect of various reagents on the different pigments found in hemochromatosis, my experience has been that of most other workers on the subject.

Hemosiderin, for example, is dissolved or disappears from sections treated with 10 per cent. sulphuric acid or with hydrochloric acid alcohol, while the hemofuscin in such sections is not appreciably affected. It may be stated, as a general rule, that the pigment which reacts readily for iron is more quickly dissolved by acids than that in which it is more difficult to demonstrate iron. The pigment in the liver cell shows its iron readily when treated with the usual reagents, and quickly disappears under the influence of acids. On the other hand, the pigment found in the thyroid responds more slowly and less certainly to the reagents used in the demonstration of iron, and sections of the thyroid show a considerable amount of undissolved pigment after treatment with acids for a time sufficient to dissolve all the pigment from a liver section of equal thickness. If the section is then treated with ammonium sulphid or potassium ferrocyanid and hydrochloric acid the undissolved residue does not give an iron reaction.

Hemofuscin entirely disappears under the influence of alkalies, sodium or ammonium hydroxid, and hydrogen peroxid, none of which has any effect on hemosiderin. Anschütz[6] states that ammonium sulphid dissolves hemofuscin. I have not found this to be the case, for in sections tested for iron by Nishimura's combination method, which involves exposure to ammonium sulphid for at least one hour the amount of hemofuscin has not been appreciably altered. Even in sections treated for one week with a mixture of ammonium sulphid and glycerin at a temperature of 60 C. (Macallum[7]), a considerable amount of the yellow pigment remains unchanged. The iron in the nuclei is well shown in sections so treated, and the fact that much, if not all, of the hemofuscin remains yellow clearly indicates that, if this pigment does contain iron, the metal exists in firmer combination than that in the chromatin of the nuclei.

Other pigments, that found in the basal cells of the epidermis and the yellow pigment in the genital organs, resemble hemofuscin in their behavior toward the solvents above mentioned. The yellow genital pigment takes on a deeper reddish tint when treated with Sudan III, but is not dissolved by alcohol, ether or chloroform.

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6. Anschütz: Ueber den Diabetes mit Bronzefärbung der Haut, zugleich ein Beitrag zur Lehre von der allgemeinen Hämochromatose und der Pankreasschrumpfung, Deutsch. Arch. f. klin. Med., Leipsic, 1899, lxxii, 411.

7. Macallum: The Distribution of Assimilated Iron Compounds, Other than Hemoglobin and Hematin, in Animal and Vegetable Cells, Quart. Jour. Micr. Sc., London, 1895-6, xxxviii, 175.

INCIDENCE

In 1899 Anschütz collected twenty-four cases of hemochromatosis with diabetes. In 1907, Futcher[8] counted thirty-five and Heller[9] forty-two, including several doubtful cases. Including those of this series and several cases recently reported very briefly by Simmonds,[10] I have been able to find about fifty cases with diabetes and thirteen which did not show diabetic symptoms.

The patients' ages are between 30 and 65 years. The patient in Heller's doubtful case died at 73.

The only well-authenticated case occurring in a woman is that reported by Abbott. Murri[11] and Berg[12] each report one other clinically, but in neither case can the diagnosis be accepted without question.

Concerning the predisposing causes little is known. Occupation seems to play no rôle. Many authors emphasize alcoholism; six exclude it as a possibility. Abbott and Beattie[13] are inclined to think that gastro-intestinal disturbances play an important part in the etiology. Many different diseased conditions appear, of course, in the former histories of this number of cases, but such is their number and diversity that no importance can be attached to any one of them.

CLINICAL FEATURES

In most cases of hemochromatosis, in the form termed *diabète bronzé* by the French, we have clinically the picture of a severe diabetes with large amounts of sugar in the urine, polyphagia, polydipsia and polyuria; extreme weakness and cachexia, generalized pigmentation of the skin, but not of the mucous membranes; and an enlarged, often tender, liver.

This association of symptoms occurs with remarkable regularity but not with absolute constancy.

Abnormal pigmentation of the skin was noted in fourteen of the twenty-four cases of which reports were collected by Anschütz, and in practically all of the authentic cases reports of which have been published since the appearance of his paper. It varies in intensity from icteric, light sun-burn, to earth-color, lead-color and the extreme bluish-black shade described by Letulle. It occurs characteristically on the face, neck, dorsum of hands and feet, extensor surfaces of forearms and legs, around

8. Futcher: Hemochromatosis with Diabetes Mellitus, Am. Jour. Med. Sc., 1907, cxxxiii, 78.

9. Heller: Ueber Hautveränderungen beim Diabète bronzé, Deutsch. med. Wchnschr., 1907, No. 30, p. 1216.

10. Simmonds: Ueber Bronze Diabetes und Pigment-Cirrhose, Berl. klin. Wchnschr., 1909, xlvi, 531.

11. Murri: Ueber Bronzediabetes, Wien. klin. Rundschau, 1901, xv, 345, 361, 406, 424.

12. Berg: Diabète Bronzé and the Pathogenesis of Diabetes Mellitus: Illustrated by a Case of Bronze Diabetes Preceded by Basedow's Disease, Med. Rec., New York, 1899, lvi, 881.

13. Beattie: Hemochromatosis with Diabetes Mellitus, Jour. Path. and Bacteriol., 1903-4, ix, 117.

the nipples and genitalia, and occasionally in the axillæ. In these regions there is an intensification of the abnormal coloring which covers diffusely and less conspicuously the skin of the whole body.

In only two of Anschütz' cases were there pigment flecks on the buccal mucosa. These appeared in Ridder's[14] recent case and in the very doubtful one reported by Murri. This is of some importance in differentiating the pigmentation of hemochromatosis from that of Addison's disease.

Anschütz states that in fourteen of seventeen cases in which this organ was described, the enlargement of the liver was clinically demonstrated. More recently Abbott and Simmonds have each reported a case in which the liver was smaller than normal (Abbott's case was one of simple hemochromatosis, without diabetes). The left lobe is sometimes enlarged disproportionately and the abdomen has been explored under the impression that the mass was that of an hepatic neoplasm.

The diabetes, as already stated, is severe and usually rapidly fatal. The history of the disease frequently begins with the symptoms of hyperglycemia; and after the onset of glycosuria, death, as a rule, occurs within a year, though cases have been reported in which diabetes was present for two or even four years (Letulle[15]) before death.

Heller in his analysis of forty-two cases gives the average amount of sugar as 4.7 per cent. and the average amount of urine excreted daily as 4.5 liters.

Several authors have noted the diminution of the glycosuria under treatment or on a mixed diet just before the exitus. In six of Anschütz' series, this symptom disappeared entirely for varying periods, as long as two months in one of Letulle's cases.

This brings us to a consideration of the cases of so-called simple hemochromatosis which do not show diabetic symptoms, such as Case 1 of this report and those of Opie, Abbott, Brault[16] (two cases), Letulle, Foa,[16] Gilbert and Grenet,[16] Richardière,[16] Osler[17] and Simmonds (three cases). With the important exception of the diabetes these cases bear a close resemblance clinically to those of true bronzed diabetes, and pathologically the two cannot be distinguished from each other.

The interpretations of these cases in the literature varies with the writers' views concerning the etiology of the affection. It is suggested by some authors that these patients may have been observed during a latent period of the diabetes, yet some of the cases were followed for

14. Ridder: Bronze Diabetes, Deutsche. med. Wchnschr., 1910, xxxvi, 36.

15. Letulle: Deux cas de cirrhose pigmentaire du foie dans le diabète sucré, Bull. et. mém. Soc. méd. d. hôp. de Paris, 1885, 406; Letulle: Note sur trois observations de cirrhose hypertrophique pigmentaire non diabétique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1897, p. 205.

16. Quoted from Hess and Zurhelle (see note 4).

17. Osler: Clinical Remarks; Hypertrophic Cirrhosis of the Liver with Bronzing of the Skin: Hemochromatosis, Brit. Med. Jour., London, 1899, ii, 1595.

fairly long periods and gave no history of polyuria, polydipsia nor polyphagia. Simple hemochromatosis is now generally held as the earlier or less severe form of the disease. Those who assume that the diabetes is due to changes in some one organ, as the liver or pancreas, hold that the lesion in that organ has not reached a sufficiently advanced grade to cause a marked disturbance in carbohydrate metabolism. Others, who believe that the three so-called cardinal symptoms, general pigmentation, cirrhosis of the liver and diabetes, are entirely independent of each other and are equally due to the same primary cause, give no explanation of these cases except that they are less severe forms.

Comparatively few records of clinical blood examinations are available, but those of the cases here reported, as well as those cited by Jeanselme,[18] Osler, Futcher and Ridder, show the red cells normal or slightly reduced in number and of normal size and general appearance. The leukocytes are not increased, nor, according to the differential counts in Osler's and Futcher's cases, do they vary especially from their usual relative proportions. The slight leukocytosis as well as the moderate anemia in Case 1 might well be accounted for by the tuberculous peritonitis.

The hemoglobin does not depart far from the normal. Margain,[19] in a rather incomplete examination without cell counts or hemoglobin estimation, noted "a certain number of red blood-cells completely deprived of hemoglobin," and in the plasma masses of free pigment. The latter observation is a very rare one. Marie[20] reports a similar one in a smear studied by Auscher, but thinks the pigment may have come from the skin, pricked to obtain the drop of blood.

The spectroscopic examination reported by Futcher showed only the usual absorption bands of oxyhemoglobin.

Lipemia is occasionally demonstrable, notably in Case 3 of this report and in Case 2 of Hess and Zurhelle.

Evidence of pancreatic disease in examination of the stools is very rare. In Anschütz' case it was quite pronounced.

Microscopic examination of a piece of skin is of great diagnostic value when one finds iron-containing pigment in the cells of the cutis and sweat glands; but no reliance can be placed on a negative report, since in some cases there is present only the iron-free pigment in the basal cells of the Malpighian layer of the epidermis as in Case 2, in Abbott's case and others.

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18. Jeanselme: Hématologie et Pathogénie du diabète bronzé, Bull. et mém. Soc. méd. d. hôp. de Paris, 1897, xiv, 179; Presse méd., 1897, p. 58.

19. Margain: Contribution à l'étude de l'origine du pigment dans le diabète bronzé et de la pathogenie de cette affection, Rev. de méd., 1905, xxv, 378; Progrès méd., 1904, xx, 472.

20. Marie: Sur un cas de diabète bronzé suivi d'autopsie, Semaine méd., 1895, xv, 229.

The three cases of this report are typical of the two well-recognized forms of the disease; Case 1 of simple hemochromatosis, Cases 2 and 3 of hemochromatosis with diabetes.

The onset in each case was rather abrupt. The patients had not noted the abnormal coloring of the skin or signs of liver disease before the appearance of subjective symptoms.

In Case 2 the pigmentation was not noted until the patient had been under observation about three weeks. In all three cases the pigmentation became progressively more intense. Heller says that in only three cases, those of Anschütz, Ubert[21] and Hyss,[21] did the appearance of the abnormal skin coloring antedate the diabetes. In one of Futcher's cases the skin had been dark-colored for several years. In Anschütz' case and in Case 1 of Hess and Zurhelle, swelling of the liver had been noticed before the diabetic symptoms. Ridder recently had a remarkable opportunity to observe the development of a case. Four years before death, pigmentation of the extremities was noted; one year later, disease of the liver was diagnosed; diabetes was present during the terminal four months.

A history of moderate alcoholism was given by each of the three patients. In Cases 1 and 3, there had been marked gastro-intestinal disturbances and dysentery ten or twelve years before.

The complication of tuberculous peritonitis, present in Case 1, has been reported several times and is perhaps second in frequency only to pulmonary tuberculosis. It is noteworthy that in both the other cases there occurred an acute parotitis. In Case 3 septicemia was demonstrated by blood-culture. In Ridder's case, also, there was an otitis media with staphylococcus septicemia and bilateral purulent parotitis. At autopsy both glands were heavily pigmented and showed numerous abscesses. These were found also in the kidneys and heart muscle.

The Wassermann reaction was negative in the two cases in which this test was applied.

PATHOLOGY

At autopsy the most striking finding is the ochre or bronze color of many of the glandular organs, the heart muscle and lymph-nodes. In addition, there is usually a much enlarged and cirrhotic liver and more or less pronounced changes in the pancreas, either a small atrophic organ or an enlarged, fat infiltrated and fibrous gland, as the case may be.

The spleen is large and firm, but varies little from its normal color. Ascites may or may not be present.

The liver is a prominent feature in any post-mortem examination: small wonder then, that, with the peculiar abnormal coloring, the cirrhotic changes, the large size and often irregular contour, this "pigmen-

21. Quoted from Heller (see note 9).

tary cirrhosis" has been regarded as of commanding importance in the pathology of the disease. Yet the changes in this organ differ but slightly from those in the pancreas. The lymph-nodes, the spleen, the heart muscle and, occasionally, other organs show fibrous change of much less degree.

Only those lymph-nodes which lie in the path of the lymph-stream from some heavily pigmented organ show in gross the ochre coloring, indicating clearly that they play but a passive part in this process.

Microscopically, the pigment remains the center of attraction. This is of several different kinds: hemosiderin or iron-reacting pigment; hemofuscin or non-iron-reacting pigment; the increased amount of those pigments physiologically present in certain situations, as that of the adrenal reticular zone, the substantia nigra, the epidermis, the interstitial cells of the testis, and the finely divided yellow pigment (described in Case 3) in the tubules of the testis, epididymis, vas deferens and seminal vesicles.

Hemosiderin is the predominant and much the most conspicuous of the pigments. The wide extent of its distribution may be seen in the report of these three cases. The characteristic sites of its deposit are in the parenchyma cells of the glandular organs and in the muscle cells of the heart. It is found in the connective tissue of an organ only when the essential cells of that organ have disintegrated and deposited it in the intercellular spaces. It occurs, also, in the lymph-nodes, in the spleen, in certain cells of the cutis, and in the endothelial cells of blood-vessels in certain situations.

Hemosiderin has no definite and fixed chemical composition, but all the granules contain iron, since this is the criterion by which they are recognized as hemosiderin. Its iron content may be readily demonstrated in gross and microscopically by the use of the usual reagents, ammonium sulphid, or potassium ferrocyanid and hydrochloric acid.

The amount of iron in certain organs, notably the liver, pancreas and lymph-nodes, is enormous. As Auscher expressed it, the lymph-nodes had been converted into veritable mines of iron.

Table 3 shows the iron content as determined in the cases of Anschütz and Hess and Zurhelle in comparison with the normal and an extreme case of siderosis in pernicious anemia by Quincke.

TABLE 3.—IRON CONTENT OF LIVER, PANCREAS AND LYMPH-NODE

	——Liver——		—Pancreas—		—Lymph-Node—	
	Dried Substance.	Ash.	Dried Substance.	Ash.	Dried Substance.	Ash.
	%	%	%	%	%	%
Normal (Oidtmann)	0.08	....	...	....	....	.....
Pernicious Anemia (Quincke)	2.1	....	...	....	....	.....
Hemochromatosis (Anschütz)	7.62	55.7	5.0	44.0	14.6	58.36
Hess and Zurhelle	7.1	....	...	....	....	.....

In these cases the liver contained almost 100 times the normal amount of iron. Hess and Zurhelle estimate the total iron in the liver of their case at 38.7 gm., about fifteen times that contained in the hemoglobin of a normal person and at least ten times that in the whole body of the average human being.

Hemofuscin varies greatly in the cases of this series. In Case 1 in the tissues examined it is hardly appreciable, scarcely more so in Case 2, while in the third case it approaches the relatively large quantity described by several other writers. The morphology differs somewhat from that of hemosiderin. It occurs in finer grains more evenly distributed throughout the cell protoplasm and has a lighter yellow color, rarely a darker brownish tint. It is found characteristically in connective tissue cells, in the capsules and trabeculæ of lymph-nodes and in the walls of blood-vessels, especially those of the lymph-nodes and gastro-intestinal canal, though von Recklinghausen describes it in the vessel walls widely distributed throughout the whole body. Chemically this pigment does not give a reaction for iron, is much more resistant to acids than is hemosiderin, and, according to Buss,[22] takes a dark stain with methylene-blue. It disappears from sections treated with dilute alkalies or with hydrogen peroxid, neither of which affects hemosiderin.

Some confusion exists regarding just what pigments should be designated as hemofuscin. Certain authors seem to consider all pigments not giving an iron reaction as hemofuscin. Since the different microchemical methods vary considerably in their efficiency in the demonstration of iron, the Perl method showing less than the ammonium sulphid or the combination of the two suggested by Nishimura, it follows that the relative amounts of hemosiderin and hemofuscin in the same tissue would vary with the method used or in the hands of different observers. It is the contention of Hess and Zurhelle, as well as of others, that no sharp distinction can be drawn between them since they find both pigments side by side in the same cell. The non-iron-reacting pigment in the glandular cells resembles hemosiderin morphologically and is quite different in appearance from that found in the trabeculæ and capsules of lymph-nodes. The two extremes at any rate have very distinct differences which have already been indicated.

Several workers have noted increased pigment in the organs where it is found under physiological conditions and say, further, that in these regions an iron-containing pigment is never deposited. This, however, does not hold true for the heart muscle cell.

So far as I know, the striking accumulation of fine yellow pigment in the sexual organs in Case 3 is unique. Hess and Zurhelle mention in the gross description of one of their cases an intense pigmentation of the

22. Buss: Ein Fall von Diabetes Mellitus mit Lebercirrhose, Pankreas-atrophie und allgemeiner Hemochromatose, Inaug. Dissertation, Göttingen, 1894.

seminal vesicles, but no microscopical examination was made, nor is there any report of other portions of the genital tract. The seminal vesicles frequently show a similar pigmentation of much less degree, especially in old or functionally inactive cases.

Increase in connective tissue is found in those organs, notably the liver and pancreas, in which great numbers of the cells have degenerated and deposited pigment in the interstitial spaces; and in the lymph-nodes and spleen, to which the pigment has been conveyed through the lymph- and blood-streams.

Individual cases of hemochromatosis present distinct differences in the distribution and extent of the lesions in various organs as may be seen by a comparison of the three cases here reported. Some idea of the grade of the process may perhaps be obtained by attention to certain details. In Case 2, for instance, the even distribution of the pigment in the liver cells with relatively few and small focal areas of extreme pigmentation; the fibrous nature of the connective tissue strands in the liver; the old sclerotic lesions in the pancreas; the degeneration of the cells in the glomerulation zone of the adrenal with pigment deposition in the interstitial tissue and the presence of this pigment in the lymphatics of the capsule; all these points together suggest to me a comparatively sluggish process of long standing. On the other hand, in Case 3, an acute and rapidly progressing lesion is suggested by the larger and more numerous focal areas of pigmentary degeneration in the liver and pancreas; by the more cellular nature of the connective tissue strands in these organs; and by the heavy pigmentation of the adrenal glomerular zone and of the cardiac fibers with little or no cellular disintegration and, consequently, no increased connective tissue.

PATHOGENESIS

Some idea of the development of the subject is of value in the discussion of its pathogenesis. These two phases will, therefore, be considered together in this section as briefly as is consistent with a clear expression of the authors' opinions.

According to Osler, Troisier, in 1871, was the first to mention bronzed cachexia occurring in diabetes.

The first description to attract attention, however, is that of Hanot and Chauffard,[23] in 1882. They described two cases of diabetes associated with pigmentation of the skin and enlarged liver. At autopsy there was cirrhosis of the liver and fibrosis of the pancreas with a great accumulation of brown pigment, both in the gland cells and in the interstitial tissue.

Quincke,[24] Tillmanns[24] and Hindenlang[24] had already described cases with rather extensive pigmentation throughout the body, associating the

23. Hanot and Chauffard: Cirrhose hypertrophique pigmentaire dans le diabète sucré, Rev. de méd., 1882, ii, 385.

24. Quoted from Opie (see note 3) et. al.

pigment deposits with severe anemias or with large extravasations of blood.

Hanot and Chauffard consider the diabetes primary and the other manifestations merely complications induced by diabetic endarteritis. Under the conditions of diminished circulation thus brought about, the liver cells produce more coloring matter than normally, leading to a deposit of pigment, a pigmentary hypergenesis. From the liver, the pigment is distributed to other organs, probably, in an embolic manner.

Letulle, in 1885, reported two similar cases and was impressed by the extreme pigmentation of the heart muscle cells and by the appearance of degeneration in the pigmented liver cells rather than any indication of activity as might be expected in a hypergenesis. The pigmentation of the cardiac fibers with little or no pigment in the interstitial tissue, he considers an unanswerable argument against the embolic distribution of the pigment from the liver. He thinks the diabetic condition induces an alteration of the blood, the pigmentation being due to a reduction *in situ* of the hemoglobin whether it be of the blood or of the different tissues.

Brault and Galliard, in 1888, follow Letulle in believing the pigment deposited wherever found in the gland cells, but emphasize the liver more strongly. They consider the diabetes and liver cirrhosis concomitant factors in the production of pigmentation. The altered blood-pigment furnished daily to the degenerated liver cells cannot be well elaborated and utilized by them and thus accumulates in the blood and in the other organs.

In 1889, von Recklinghausen, under the name of "general hemochromatosis," described a wide-spread accumulation in the organs of an iron-containing and an iron-free pigment, both of which he regarded as derived from hemoglobin, together with cirrhotic changes in the liver and pancreas. Most of the glands of the body were of a deep brown color and in their secreting cells he found the iron-containing pigment, which he called hemosiderin.

He named the iron-free pigment occurring in finer granules, hemofuscin, and describes it in smooth muscle cells of the stomach and intestine, of the blood-vessels and lymphatics, and rarely in those of the urinary bladder, ureters and vas deferens; also in certain connective tissue cells, those of Glisson's capsule, the splenic trabeculæ, and the sheaths of blood-vessels. He described these peculiar findings as occurring in the course of different diseases, and gives diabetes as the cause in one case.

Buss, in an inaugural dissertation published in 1894, reported a case having clinically the characteristics of the *diabète bronzé* described by the French, and which in its pathology was the exact counterpart of the hemochromatosis of von Recklinghausen. He discussed the then recent work on pancreas extirpation and its relation to glycosuria and considered the hemochromatosis, caused by some primary blood disease of

unknown origin, to be the predisposing cause of diabetes, which was induced by the severe pancreatic changes.

Marie, in 1895, says we must look to the hemoglobin of the blood and tissues for such quantities of iron. In his opinion, the following is the sequence of events: dissolution of the hemoglobin of the blood under the influence of a general primary cause; transformation of the hemoglobin into pigment granules by the action of the cellular protoplasm of the organs; exaggerated elimination and accumulation of the pigment in the organs by irritation and consequent atrophy of the cells; supplementary elimination of the pigment by way of the lymph-channels with irritation of these channels and the production of a sclerosis of the interstitial connective tissue; and overloading of the lymph-nodes with pigment.

He deplored the prevailing opinion that bronzed diabetes was an accident or termination of ordinary diabetes. Some of his predecessors had spoken of it as pigmentary cirrhosis in diabetes, others as bronze cachexia in diabetes. To him, it was a true clinical and pathological entity, as distinct from the ordinary form as was, in his opinion, pancreatic diabetes, with which he would classify it rather than with any other form.

Acard,[24] Dutournier[24] and Jeanselme in their publications on the subject during the next two years, agree in all essentials with Marie.

Rendu and de Massary[25] in 1897, laying emphasis on cases of malaria reported with extensive pigmentation, conclude that the iron pigment, due to the particular action by the cellular protoplasm of a glandular organ or of a cardiac cell on hemoglobin, is the result of a general cachexia of the organism, and that this cachexia may be caused by diabetes complicated with a cirrhosis of the liver, by an hepatic disease alone, or by the malarial intoxication.

In 1899, Anschütz published his very comprehensive paper in which he reports a case of his own with thorough pathological investigations, and collects and tabulates in an interesting way the twenty-four cases of bronzed diabetes published up to that time. In his opinion, the blood destruction of unknown origin is primary. At the same time, there is a diseased condition of the cells of the glandular organs, which, under some mysterious influence, take up and hold tremendous amounts of the products of blood destruction and undergo a gradual degeneration. In those organs in which the degeneration is most pronounced, there occurs a reactive inflammation resulting in connective tissue growth. The diabetes is a result of the extensive lesions thus induced in the pancreas.

He remarks that "it is certain that a definite and significant blood dissolution occurs," that without very active new blood formation such large amounts of pigment could not be deposited. He is naturally surprised and somewhat nonplussed that there is never any sign of anemia,

25. Rendu and de Massary: Cirrhose et Diabète Bronzé, Presse méd., 1897, p. 58.

that the brain and kidneys contain almost no pigment and the spleen relatively little.

In the same year, Opie, after an admirable presentation of the subject, closes his paper with the following conclusions:

"1. There exists a distinct morbid entity—hemochromatosis—characterized by the wide-spread deposition of an iron-containing pigment in certain cells and an associated formation of iron-free pigments in a variety of localities in which pigment is found in moderate amount under physiological conditions.

"2. With the pigment accumulation there is degeneration and death of the containing cells and consequent interstitial inflammation, notably of the liver and pancreas, which become the seat of inflammatory changes accompanied by hypertrophy of the organ.

"3. When chronic interstitial pancreatitis has reached a certain grade of intensity, diabetes ensues and is the terminal event in the disease."

He thinks it possible that some primitive alteration of the blood, associated with intravascular destruction of red corpuscles, precedes the pigment deposition.

Two years later, Abbott reported the first case of hemochromatosis occurring in a woman. Diabetes was not present. Pathologically, the descriptions are typical of the disease except that the pigmentation was perhaps a little less widely distributed than usual (none in suprarenals or kidneys, little in skin) and the liver was slightly smaller than normal.

Her view is that some unknown primitive agency is at work on the red blood cells and on the parenchymatous cells of certain organs leading to the pigmentation. The cirrhosis results as a chronic interstitial inflammation from the presence in the tissues of the pigment set free by destruction of the parenchymatous cells. She is inclined to emphasize gastro-intestinal disturbances in the etiology and is rather doubtful as to the propriety of accepting this disease as a pathological entity.

During this year, Murri reported, from a clinical standpoint, a unique case. The patient, a woman 59 years old, for fifteen months had experienced symptoms of diabetes and a darkening of the skin. The urine contained from 2 to 4.5 per cent. of sugar; the skin pigmentation seemed fairly typical of bronzed diabetes with the exception of pigment flecks on the buccal mucosa, but there was no sign or symptom of lesions in the liver, pancreas or spleen. At different times there were abdominal pain and pains in the groin radiating to the abdomen and leg. There was no fever. A piece of skin with subjacent lymph-node was removed and found to contain a considerable amount of pigment, some of which gave a doubtful iron reaction. After the administration of epinephrin tablets was begun, the urine became sugar-free. The patient's condition remained the same for a while, then rapidly improved and, within less than a year after entering the hospital, she was discharged with most of

her weight regained, her urine physiological, and the abnormal skin pigmentation entirely gone. In 1901, she had remained well for two years.

As Murri says, this is undoubtedly a case of bronzed diabetes if we accept the name literally, but very unlike the disease as usually described. It is the only case on record of recovery, but its relation to hemochromatosis is not sufficiently established to give it a place among the well-authenticated cases of this disease.

Murri holds that the frequent occurrence together of the three phenomena, diabetes, hemochromatosis and cirrhosis of the liver, is not to be explained on the assumption that the process from which they arise is an individual and peculiar one; but that the disease processes, which are peculiar to each of the phenomena, possess certain characteristics which are partly biological (age), partly hygienic, partly toxic, and partly of diseased nature, but all of which reach a climax in an injury to the household of general metabolism.

The rational conclusion is on the hypothesis, he says, of a general dystrophy of the cell elements of the body, brought about by long continued action of the causes which are at work injuring their metabolism. This dystrophy goes along with the diminution of a normal capacity, namely, the oxidation of carbohydrates, and with the occurrence of two abnormal properties. The one consists in the capacity of the tissues to absorb and fix blood coloring material, the other in the increase of connective tissue, which, especially in the liver, assumes the character of an interstitial inflammation.

In common with Murri, most of the other German writers in the past decade, Hess and Zurhelle, Aschoff and Hess,[26] and recently Simmonds and Martineck,[27] hold that the three striking phenomena of the disease, diabetes, hemochromatosis and cirrhosis of the liver, are independent of each other and are each referable to the same common cause. They emphasize alcohol as a most important etiological factor.

Ridder considers a disease of the liver cells primary and follows Anschütz in his opinion as to the causes of the cirrhosis and diabetes.

Beattie, writing in 1903, is impressed by the possibility of a toxic agent derived from the intestine by way of the portal circulation, causing a degeneration of the cells of the liver, pancreas and other glands and at the same time a cirrhosis of these organs. The pigment, he thinks, is due partly to the inability of the degenerated cells to perform properly their metabolic processes and partly to transportation from the liver and pancreas. While the cirrhosis is, in his opinion, due, chiefly, to the toxic degeneration of parenchyma cells, it may, in part, be due to irritation produced by the pigment in the tissues.

26. Aschoff and Hess: Clinical Presentation of a Case of Hemochromatosis, Berl. klin. Wchnschr., 1894, xli, 1231.

27. Martineck: Zur Pathogenese und klinischen Diagnose der Diabète bronzé, Charité Ann. Berl., 1909, xxxiii, 40.

Parker,[28] reporting a case in the same year, is the only author who in so many words questions the occurrence of an abnormal blood destruction and suggests that the chief factor may be a loss in the power of elimination of certain iron-containing products rather than any abnormal amount of hemolysis.

He, in common with Heller and Martineck, mentions a supposition concerning the pathogenesis of hemochromatosis which they attribute to Croftan. I have been unable to find it in the elaborate form given by them in any of the references to Croftan's[29] work which they cite.

Croftan finds a ferment in liver extracts which he considers identical with trypsin, which has the power of breaking up both sugar and hemoglobin in the presence of each other, but is without effect on either, should the other be absent. According to the authors just named, the supposition is that some toxic agent produces a degeneration and chronic inflammatory changes in the liver and pancreas. When the pancreatic changes have reached such a grade of intensity that there is an insufficiency of the ferment trypsin, hyperglycemia results. Under the influence of this increased sugar content of the blood and in the absence of trypsin, the hemoglobin is changed into hematochromatin. The normal liver has the power of removing this abnormal pigment, but the cirrhotic liver lacks this ability; hence occurs the accumulation of iron-containing pigment in the liver and other tissues.

Rössle,[30] in 1906, reported a remarkable case of a patient 29 years old, who died in coma a few hours after entering the hospital. Pathologically, there were found cirrhosis of the liver, wide-spread lesions of the capillaries with many small hemorrhages, and, most remarkably, phagocytosis of the red blood corpuscles by the parenchyma cells. These unique findings were observed in the liver and kidney especially, to less extent in the pancreas, and not at all in the other organs. The pneumococcus was isolated from the tissues at autopsy.

He reviews the literature of hemochromatosis and considers his case as the earliest form yet observed. The primitive cause, in his opinion, is an acute infection with wide-spread "capillaritis" resulting in hemorrhagic edema and phagocytosis of the blood corpuscles by the parenchyma cells. The subsequent change of the hemoglobin to hemosiderin produces the siderosis of those cells. There is a rapid regeneration of the blood to normal after the acute stage has subsided. The cirrhosis may be due

28. Parker: Case of Bronze Diabetes, Brit. Med. Jour., 1903, ii, 1052.

29. Croftan: Some Experiments on the Formation of Bile Pigment and Bile Acids; A Contribution to Our Knowledge of Icterus, Phil. Med. Jour., 1902, ix, 75, 143; An Experimental Investigation into the Causes and Treatment of Diabetes Mellitus, Am. Jour. Med. Sc., 1902, cxxiii, 662.

30. Rössle: Ueber Phagocytose von Blutkörperchen durch Parenchymzellen und ihre Beziehung zum haemorrhagichen Oeden und zur Haemochromatose, Beitr. z. path. Anat. u. z. allg. Path., 1907, xli, 181.

partly to the "capillaritis" and partly to the destruction of the parenchyma. Diabetes is a terminal symptom.

This view is of interest because it departs so strikingly from those usually given and is founded on an observation which is interesting of itself. But he fails entirely, it seems to me, to substantiate his claim that there is any connection whatever between his unique case and those of hemochromatosis.

Several attempts have been made to reproduce the disease in animals experimentally by injecting blood into the peritoneal cavity and by producing intravascular hemolysis by the use of poisons such as toluylendiamin; but such procedures have failed to produce anything but the faintest analogies to hemochromatosis.

Auscher and Lapique[31] and, later, Meunier,[32] produced, in this way, heavy pigmentation of the spleen, bone-marrow and abdominal lymph-nodes with less pigment in the liver. By increasing the amount of blood injected the disparity between the spleen and liver pigment deposits was diminished and they considered that they had reproduced the disease. There was never any connective tissue growth nor any reaction whatever, even when the spleen contained a much greater amount of iron than is found in any case of hemochromatosis.

The most thorough work of this kind, of which I know, is that of Biondi,[33] who poisoned dogs, cats and guinea-pigs with toluylendiamin administered by mouth and subcutaneously. In this way he produced anemia, jaundice and, sometimes, hemoglobinuria. Pigment deposits were found in the liver, spleen, bone-marrow and lymph-nodes, and occasionally in the kidney and other organs. He thinks that in any case of hemoglobinemia the liver cells increase their secretion of bile (*Pleiochromie*) and perhaps to such an extent as to cause jaundice without any obstruction of the bile-passages. The other part of the hemoglobin molecule, the iron-containing portion, is taken up by the leukocytes, giving rise to what he calls *siderifere Zellen*, and in this way to siderosis. These cells are carried through the blood to the spleen, bone-marrow, lymph-nodes and other organs. He says, therefore, that siderosis is the anatomical exponent of bile secretion. (He found a certain amount of iron pigment normally present.) Only when the liver cells were degenerated and manifestly abnormal did he find hemosiderin within their protoplasm. He thinks the diseased cell has lost its normal capacity of ridding itself of the iron-containing portion of the hemoglobin molecule. The

31. Auscher and Lapique: Quelques recherches chimiques sur un cas de diabète pigmentaire, Compt. rend. Soc. de biol., 1895, 402, 510; 1898, 185.

32. Meunier: Contribution expér. à l'étude pathogenique de la cirrhose pigmentaire, Thèse, Paris, 1898.

33. Biondi: Experimentelle Untersuchungen über die Ablagerung von eisenhaltigem Pigment in den Organen infolge von Hämatolyse, Beitr. z. path. Anat. u. z. allg. Path., 1895, xviii, 176.

siderosis of the liver cells, then, he says, is an expression of their alteration. Anschütz thought this a particularly happy statement of the case and apparently considered this portion of Biondi's work applicable to the parenchymatous siderosis in hemochromatosis. The picture which he draws of the general siderosis in these experiments has little or no resemblance to that of hemochromatosis.

Most authors who express an opinion on this point think that, in addition to some injury to the parenchyma cells, an increased blood destruction is an essential factor in the production of such heavy pigment deposits. Others seem tacitly to accept this prevailing opinion.

Meltzer[34] has suggested that by some fault in the mechanism of iron metabolism by which this metal is excreted, the organs and cells of the body retain all or most of the iron which reaches them on its normal round through the body. Parker, also, asks the question whether it may not be possible that the essential factor is a failure in the elimination of iron rather than an increased hemolysis.

Since the work of M. B. Schmitt,[35] it has been generally accepted that all iron-reacting pigments have their origin from hemoglobin, and that, although a pigment fails to respond to the available microchemical tests, it cannot be said that it does not contain iron. According to Schmitt, the iron-reacting pigment represents only a stage in the continual development which these pigments are undergoing. Hemofuscin, then, is really the older state of the same pigment, which at an earlier period would have given a positive reaction for iron. By a further elaboration of this conception, Schmitt comes to the conclusion that melanin is a still later stage beyond the hemosiderin and hemofuscin period.

Many workers in metabolism experiments have proved that iron salts, whether organic or inorganic, administered by mouth, subcutaneously or intravenously, cause a deposit of an iron-reacting pigment in various parts of the body without any evidence of blood destruction. Wells,[36] in speaking of melanin, after mentioning the fact that the amount of iron present is usually extremely small, and often is entirely absent, says: "Furthermore, the presence of iron is no proof that the pigment is derived from hemoglobin, since many other proteids contain iron."

That iron forms an integral part of various tissues of the body and exists in firmly bound organic form is certain. Especially in nuclein substances iron has been found in relatively large amounts. According to Hammarsten,[37] a large amount of proteid substance of the liver exists

34. Meltzer: The Pathogenesis of General Hemochromatosis (Diabète Bronzé), Med. Rec., New York, 1900, lvii, 43.

35. Schmitt: Ueber die Verwandtschaft der hämatogenen und autochthonen Pigmente und deren Stellung zum sog. Hämosiderin, Virchows Arch. f. Path. Anat., 1889, cxv, 397.

36. Wells: Chemical Pathology, W. B. Saunders Co., 1907, p. 393.

37. Quoted from Meinertz: Ueber den Eisenstoffwechsel, Zentralbl. f. d. ges. Physiol. u. Path. d. Stoffwechs., 1907 (new series), ii, 652, 689.

as an iron-containing nucleoproteid. Zaleski[37] isolated such a combination and called it "hepatin." Schmiedeberg[37] described an iron-containing nucleoproteid, rich in nucleic acid, "ferratin," which on hydrolysis yields a nuclein base, a pentose and levorotatory xylose.

What function tissue-iron serves is not well known. Schmiedeberg considers ferratin as reserve iron for blood formation. He gets a diminution in the ferratin content of the liver by the administration of iron-poor food and by repeated blood letting. It is known that in many chemical reactions iron is very potent as a catalyzer and in recent times catalytic reactions in the organism are being looked on with increasing favor. Spitzer[37] ascribes to iron a definite rôle as an oxygen-carrier. The oxidizing power of water extracts of the liver is due, according to him, to an iron-containing nucleoproteid, which is contained also in other organs. Iron is found in both split products, the nucleic acid and the proteid; both are oxygen carriers. In further splitting, the oxidizing power persists as long as the split products contain iron.

Dastre and Floresco[38] accept the oxygen-carrying capacity as an important function of liver iron. They show that in certain invertebrates, the cephalopodia for example, the liver, so important in metabolic combustion, is rich in iron. The blood, on the contrary, does not contain iron. In these animals, certainly, the tissue iron is entirely independent of blood destruction, whatever may be said of the higher species.

A. B. Macallum,[39] basing his results on microchemical tests devised by himself, states that iron is found in all nuclei in amounts proportional to the chromatin. Assimilated iron is present in the cytoplasm of cells in higher animal forms in yoke-holding ova, the cells of yoke-holding embryos, and the hematoblasts of vertebrates. In addition, iron occurs in the cytoplasm of *ferment-forming gland cells of all descriptions.*

It is precisely in these ferment-forming gland cells that hemosiderin is deposited most characteristically in hemochromatosis.

In the majority of the cases in the literature, no blood examinations are reported. There are, however, some available figures. An average of four red cell counts made in the three cases of this series shows 4,709,000 cells per cubic millimeter. The hemoglobin estimations by different methods never fell below 90 per cent. Jeanselme gives as the first count in his case 3,379,000 red cells with 90 per cent. hemoglobin. Eight days later, one week before death, the count was 3,308,000. He noted no abnormal nucleated cells. The coagulability of the blood and retraction of the clot were normal. Spectroscopic examination of the blood serum showed no hemoglobin.

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38. Dastre and Floresco: Function martiale du foie chez tous les animaux en général, Arch. de physiol. norm. et path., 1898, x, 176.

39. Macallum: See note 7; also Die Methoden und Ergebnisse der Microchemie in der biologischen Forschung, Ergebn. d. Physiol, 1898, vii, 552.

In Futcher's two cases, the counts were 4,800,000 and 5,304,000 with the hemoglobin 87 per cent. and 95 per cent. respectively. Spectroscopic examination of the blood in the second case, made by Dr. Walter Jones, showed only the normal absorption bands of oxyhemoglobin. In this case the urine was examined for hematoporphyrin as a test of blood destruction, but this substance could not be demonstrated.

In Osler's case, the red cell count was above normal and no nucleated reds were seen in a differential count of 200 white cells. Ridder gives two red counts in his case, 4,800,000 and 4,400,000, with normal proportions in two differential counts of the leukocytes.

The bone-marrow of the femur was examined in two of my cases. Case 2 shows practically a normal picture. The marrow in Case 3 is slightly hyperplastic, but there is nothing to indicate any unusually active hematopoiesis.

Insignificant purpura has been described in a few cases, epistaxis in others and hemoglobinuria in one. These findings have been emphasized by different writers. The majority of the reported cases, however, show no such lesions.

Having failed to find in the clinical examination of the blood and in the histological appearance of the hematopoietic organs any reason to believe that there is a primary pathological blood destruction or blood alteration of any kind, we will direct our attention to the iron compounds of the tissues.

That increased blood destruction is not necessary to account for the large amounts of iron found in the tissues in this disease may be shown by a simple calculation, provided we assume a marked retention of the iron which is normally excreted. Iron excretion occurs, principally, by way of the alimentary tract and, to less extent, in the urine in cases of blood or tissue destruction. The question of its retention should be thoroughly investigated by chemical studies during the clinical observation of the patient.

Hess and Zurhelle estimated the total iron in the liver of their case, which contained a very high percentage, at 38.7 gm. Twelve additional grams for the pancreas, heart, lymphatic tissue, etc., is certainly a liberal allowance. This gives us 50 gm. of iron accumulated in the body. The whole amount of blood in the body of a man is said to contain about 2.4 gm. of iron. It is estimated that one-tenth of the red blood corpuscles undergo dissolution physiologically each day, thus liberating 0.24 gm. of iron. At this rate, if little is lost by excretion, 50 gm. of iron might be accumulated in less than seven months, which would be a very short course for the disease judged even by the period of active symptoms.

We may suppose that under some unknown influence there is a change in the equilibrium of the different cell constituents and under the changed conditions certain chromogenic groups of the proteid molecule can no

longer be held in the usual chemical and physical form and are deposited in the shape of pigment granules. The important cell constituent thus lost is being constantly replenished in the case of the glandular organs from the iron-containing portion of the hemoglobin molecule derived from the physiological dissolution of red cells in the circulating blood. Different cells are affected in varying degree. Newly regenerated cells may resist for a while, but on becoming physiologically active, they, too, suffer from the same pathological process, but of course, show much less pigment than their fellows (Fig. 6).

There is, then, a cell degeneration leading in the most active cells to dissolution, due both to the pigmentary degeneration of the protoplasm and to the accumulated pigment acting as a foreign body within the cell membrane. Differences in the chemistry of different cells could account for the chemical differences in the pigment found.

I would regard the sclerosis in different organs as a result of chronic interstitial inflammation produced, as Opie says, by two factors: pigmentary degeneration of the parenchyma cells and irritation produced by the presence of the pigment in the interstitial tissue. The latter factor is well illustrated in the lymph-nodes where the amount of fibrous tissue is roughly proportional to the pigmentation, and where in some cases (Case 1) foreign body giant cells are easily found.

The pathology of diabetes is a much mooted question. Naunyn and a few others have ascribed the diabetes in this affection as well as in common diabetes to cirrhosis of the liver. Palma, Von Noorden and others hold that diabetes and liver cirrhosis occur together so rarely that they cannot be considered more than the coincidence of two common diseases.

The relationship of chronic interstitial pancreatitis to diabetes has been fairly well established, and according to Opie, Anschütz, Marie and others, it is in the pancreas that one must look for the cause of the diabetes of hemochromatosis. In practically all the cases which are reported in sufficient detail, there have been more or less pronounced lesions in the pancreas. Yet what pathologist would be willing to say from an examination of that organ whether or not diabetes had been present? It is true that in Case 1 (simple hemochromatosis) the pancreas is more nearly normal than those of the other two cases, yet, it is in the islands of Langerhans in Case 1 that the pigment in the pancreas is most marked (Fig. 2). These structures seem relatively unaffected in the other cases which showed diabetes. Again, the pancreas from Case 3, a marked diabetic, seems less severely diseased than that of Opie's case, sections of which I have had the opportunity of examining. In his case, sugar was never present in the urine, nor were there ever any other symptoms of diabetes.

Emphasis has already been laid on the probable function of the iron-containing tissue compounds as catalytic agents, especially in oxidizing processes. There are, apparently, serious disturbances among these compounds in hemochromatosis. It is not surprising, therefore, that we find a diminution of the capacity of the organism to oxidize carbohydrates, without looking for further gross changes in any one organ. This view, it seems to me, would harmonize better with those cases in which the sugar disappears from the urine for varying periods. The process as outlined above, need not necessarily be continually active, nor present always in the same degree. It may well be that fluctuations occur and that the periods of lessened activity in the morbid process become manifest in a diminution or disappearance of the glycosuria and perhaps improvement in other ways. Similarly, in those cases in which the process is sluggish from the beginning, glycosuria may never appear and abnormal metabolism along other lines produce the weakness and cachexia of these cases of simple hemochromatosis.

Concerning the unknown influence which inaugurates the pigmentary changes and the mechanism of the pigment deposit, very little can be said at present.

Opinions concerning the origin and deposition of melanins, the most extensively studied pigments, have undergone radical changes in recent years. They are no longer regarded as being composed of the products of hemoglobin, but rather as having an origin in albumin, especially in those products with an aromatic or heterocyclic nucleus (tyrosin, etc.). It is thought that from these, under the action of various oxidizing ferments, the melanotic pigments are formed. Gortner[40] has recently demonstrated that the pigmentation of the integuments of the larva of *Tenebrio molitor* is the result of the interaction of an oxydase and a chromogen. The process of coloration is capable of preceding in the absence of life, but ceases entirely if the enzyme is killed by heat or if oxygen is withdrawn.

Brown[41] has recently shown that hemosiderin may be produced outside of the animal body and is increased in the liver of rabbits during autolysis for a period of from twenty-four to forty-eight hours. Since this post-mortem hemosiderin formation is most marked in parts of livers exposed to the air, he concludes that the hemosiderin is an oxidation product of hemoglobin due to enzyme action.

In view of the fact that physiological pigment deposits may be due largely to enzyme action, we may consider this as a possibility, at least, in the abnormal pigmentation of hemochromatosis. Gortner says of the

40. Gortner: Origin of the Brown Pigment in the Integuments of the Larva of Tenebrio Molitor, Jour. Biol. Chem., 1910, vii, 365.

41. Brown: Changes in the Hemosiderin Contest of the Rabbit's Liver During Autolysis, Jour. Exper. Med., 1910, xii, 623.

larva of *Tenebrio molitor* that the chromogen is present in very small quantity and is probably secreted only as needed for the pigmentation, while the oxydase is constantly present in relatively large amounts. Perhaps the relations are much the same in human tissues and perhaps excessive chromogen is formed as an intermediary product in the peculiar degeneration of the cell protoplasm; and, acted on by the ever-present oxydase, is precipitated as pigment granules. This may be one explanation of the changes seen in the rabbit's liver during autolysis and some experimental work now in progress indicates that such may be the case.

SUMMARY

Hemochromatosis is a distinct morbid entity characterized by the wide-spread deposition of an iron-containing pigment, especially in the secretory cells of glandular organs, by the presence of an iron-free abnormal pigment in certain situations, and by an increase in the pigmentation of those localities which contain pigment under physiological conditions.

There is no evidence of any abnormal blood destruction or of reparatory activity of the hematopoietic organs.

Hemochromatosis may be considered a metabolic disease implicating many of the body tissues and manifested, especially, by a change in the chromogenic groups of the proteid molecule with the deposition of pigments.

As a result of the pigmentary degeneration and the accumulation of pigment in the interstitial tissue, there occurs a reactive inflammation with a fibrosis of various organs.

The diabetes may be referable to the diminished exidative powers of the body due to the pronounced disturbance in the iron-containing constituents of the tissues, assuming these iron compounds to be catalytic agents in oxidizing processes.

There is no constant predisposing cause.

In conclusion, I wish to express my appreciation to Professors Barker and Thayer for the privilege of using the clinical histories, and especially to Dr. G. H. Whipple for his unfailing interest during the course of this study and for valued suggestions in the preparation of this paper.

Johns Hopkins Hospital.

BOOK REVIEWS

DYSPEPSIA: ITS VARIETIES AND TREATMENT. By W. Soltau Fenwick, M.D., Doctor of Medicine of the University of Strassburg. Cloth. Price, $3 net. Pp. 485, with illustrations. Philadelphia: W. B. Saunders Co., 1910.

The title of this book emphasizes an interesting change in medical thought. Not many years ago it was considered an evidence of ignorance to use the term "dyspepsia;" anatomical names for diseases were considered the only ones proper for scientific men. So it was that the diagnosis of chronic gastritis flourished. But methods of investigating functions enabled us to get a good deal of light on functional alterations in the stomach, and we can now use a functional term, well realizing that the recognition of a functional alteration does not imply the absence of anatomical changes, but rather the reverse. So, also, we are willing to take so general a term "dyspepsia" as a convenient designation for certain important conditions and use it as a basis for further work. Dr. Fenwick gives an interesting study of a very large amount of clinical material, 18,000 cases, in fact; though for the purpose of this book 1,000 cases taken in equal proportions from hospital and private practice were utilized. The book has a very strong personal character; the main thesis is that dyspepsia is not a "substantive disease dependent on the primary failure of gastric functions," but that "in a large proportion of cases symptoms originate entirely in the intestines and ensue from a derangement of the liver, pancreas or bowels." Fenwick also thinks that stomach dyspepsias are rarely primary, "but usually a consequence of a serious disease of another and perhaps remotely situated organ." The author reiterates these views in various ways, and although they will not strike some readers as being entirely original, there will undoubtedly be a definite gain from the belief in the complexity of dyspeptic alterations. Some older teachers fixed the same idea with illustrations of "vicious circles." The author's preface furnishes a guide to the understanding of the work and deserves careful study for that reason as well as for its many suggestive ideas. All who have had experience in the subject can confirm the statement that the "science of gastric diagnosis is the art of taking trouble." The analysis of a thousand cases shows some interesting variations in the existence of dyspeptic diseases; for example, hyperacidity he found twice as prevalent in his private practice, hypersecretion and hyperesthesia six times as prevalent in hospital practice. Gastric neurasthenia was four and a half times as prevalent in hospital practice. Gastroptosis occurred to the extent of 3 per cent. in hospital practice and 17.6 in private practice. The author gives a scheme for the analysis of cases of dyspepsia that has the fault of all similar schemes: it suggests an idea of simplicity, comparable to that in the case of plant analysis, which the advanced student realizes, does not correspond to actual conditions. The author's classification of dyspepsia does not differ essentially from others generally used. He distinguishes secretory, motor, nervous and inflammatory alterations, ptoses, those due to foreign bodies and living creatures (the latter being dealt with rather cursorily); then the dyspepsias of infancy and old age, and those due to diseases of other organs. All through the work we see evidence of large personal experience and careful study. The chapters on hypersecretion, chronic gastritis and gastric neurasthenia are mines of information. The chapter

on achylia gastrica, on the other hand, will seem to many to be too short. The chapter on dyspepsias in various diseases and that on intestinal indigestion should be very helpful in the practical management of those conditions. The general practitioner as well as the advanced student will be able to derive much benefit from the work, and even the stomach specialist will find many interesting experiences and suggestions. The mechanical preparation of the book is very good and the proofreading in general excellent. Exception might be taken to certain nostrums mentioned with approbation. Surely they could be replaced by official preparations.

DIAGNOSTIC AND THERAPEUTIC TECHNIC. A Manual of Practical Procedures Employed in Diagnosis and Treatment. By Albert S. Morrow, A.B., M.D., Adjunct Professor of Surgery in the New York Polyclinic. Cloth. Price, $4 net. Pp. 775, with 815 illustrations. Philadelphia: W. B. Saunders Co., 1911.

The author of this book truly says that there is no single book on the same lines. In Germany the two books of Gumprecht and Rieder cover the same lines, but are not, of course, widely useful in English-speaking countries. The present work combines descriptions of both diagnostic and therapeutic methods, in greater detail than is possible in works on practice. It is, therefore, especially useful to interns and young practitioners, but on account of the completeness with which the matter has been brought up to date, the book is likely to be of value also to experienced practitioners and teachers. No method of value seems to have been omitted and in general the directions are clear, full and accurate. Much of the material is such as is usually considered in works on minor surgery and it is perhaps natural that those chapters should be proportionately larger than others, but there is little actual cause for criticism in this respect. The remarks on blood-pressure are, perhaps, sufficient for anesthetists, but not for internists or general practitioners. Only one method of determining diastolic pressure is given, and the importance of that determination seems underrated. Scarification is recommended for vaccination, and a denudation of ⅛ to ¼ inch in diameter is recommended. Surely if the lymph is as good as it should be, so extensive an operation is not necessary. It is said that incisions draw too much blood, but why they should draw more blood in the United States than in other countries is not explained. Shields and gauze are recommended for protecting the lesions without any explanation of their dangers. The possibility of complications, such as cellulitis, deep ulcers and erysipelas is mentioned, but the proper treatment for these complications is not even mentioned, nor its necessity emphasized. Tetanus seems to be attributed only to errors in the proportion of lymph. Surely it is much more important to call attention to the danger of infection after the operation. The directions for aspirating are excellent, but the illustration represents the preliminary puncture as unnecessarily large. Intratracheal injections are not mentioned; perhaps they are considered too special for such a work. The advice to use glycerin on the stomach-tube before passing is antiquated. The description of normal urine should hardly be necessary in a book of this kind, but if it is considered so a wider range of specific gravity than 1018 to 1022 should be stated. Among occasional obscurities of language that regarding hydrochloric acid in cancer of the stomach may be mentioned. The reviewer gathers the impression that free hydrochloric acid must be constantly absent in order to make the diagnosis. Some very important cases will be missed if that is done. The dosage given illustrates the difficulty with which the metric system makes its way. One of the chief advantages of the metric system is the simplicity with which solutions

can be made. The directions in this book would lead one to think that there is some special potency in complicated figures. How else are we to explain directions for making solutions for intravenous injection by taking 0.92 to 1.9 gm. of salt and 473.11 c.c. of water. Imagine, too, the timid mother measuring out 59.2 c.c. of castor-oil and 118.4 c.c. of "warm soapy water!" She should be as much impressed with the accuracy of the prescriber as the latter is when he writes gm. 0.324 of bismuth subnitrate or gm. 31.10 of starch.

The criticisms are few in comparison with the large amount of really useful material in the book. The numerous illustrations are well chosen and pleasing. Altogether a wide and satisfactory use is to be predicted.

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CEREBROSPINAL MENINGITIS DUE TO BACILLUS INFLUENZÆ

A REPORT OF TWO CASES, FROM ONE OF WHICH THIS ORGANISM WAS OBTAINED IN PURE CULTURE FROM THE CIRCULATING BLOOD EIGHTY-FIVE DAYS BEFORE DEATH *

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Nervous phenomena in influenza are very common, but if we are to judge from the cases reported in the literature, meningitis due to *Bacillus influenzæ* alone is uncommon.

Cohoe[1] in 1909 reviewed the cases that had been reported up to that time and added one case of his own. He was able to collect reports of twenty-four cases in which the diagnosis was based on bacteriological findings. Fifty-six per cent. of these cases occurred in children under 1 year of age. Eighty-five per cent. of the patients in Cohoe's review died; most of the cases came to autopsy. During the past two years several new cases have been reported.[2]

The gross changes in the central nervous system of patients dying from influenzal meningitis have shown great variation in their situation, extent and character. In most cases the lesions are confined to the tissues of the meninges but the gray and white matter of the brain and cord may be involved. The meningeal involvement is generally confined to the cerebrum, and the extent of the lesions in this location varies greatly. In some cases only very small areas, in others the greater part of the cerebral meninges, are affected. The gross character of the lesion in the meninges is not constant. In some of the cases no gross pathological changes could be seen; in others there was only congestion of the blood-vessels; but there may be frank exudate, indistinguishable from that produced by the pneumococcus or meningococcus, intrapial ecchymoses, or large or small intrapial hemorrhages. The macroscopical changes in the gray and white matter of the brain and spinal cord vary with the

*Read before the American Association of Bacteriologists and Pathologists, May, 1910.

1. Influenza Meningitis. Am. Jour. Med. Sc., 1909, cxxxvii, 74.

2. Davis, Tr. Chicago Path. Soc., 1910, viii, 39-44, reports seven cases of influenza meningitis. From two of these cases *Bacillus influenzæ* was obtained in pure culture. Meyer in an article entitled: Ueber akute genuine Encephalitis, Frankf. Ztschr. f. Path., 1910, v, 532, gives reference to several articles on influenza infections of the central nervous system.

extent and character of the lesion. In a good many cases no gross changes are evident but there may be congestion of the blood-vessels, pale to bright red areas of softening of varying size and number, or even abscess formation in the brain. The cerebrospinal fluid may be perfectly clear, slightly turbid, or very cloudy.

The comparatively few reported cases of cerebral infection with *Bacillus influenzæ* may in part be explained by the fact that this organism grows with difficulty and may be present without producing recognizable gross changes. The correct diagnosis in such cases may easily be overlooked unless bacteriological methods suitable for the isolation of *Bacillus influenzæ* are employed and a thorough histological examination made. With the proper care *Bacillus influenzæ* can be obtained from the greater per cent. of the cases in which it is present, but small areas of encephalitis may easily be overlooked. These areas may be very few, very small, and limited in their distribution. In such cases, unless sections from numerous locations are examined, the lesions may not be found.

Cerebrospinal fluids removed during life or central nervous systems that at autopsy show definite pathological changes will scarcely pass without careful bacteriological examination, but often the special media necessary to grow *Bacillus influenzæ* are not employed. But the cases that deserve special attention are not so much those that show definite pathological changes of the central nervous system as the ones that show little or no gross lesions. It is not uncommon to find little or no gross change in the central nervous system of patients who showed definite signs and symptoms of acute cerebral involvement, and the cerebrospinal fluid removed from such cases during life very often appears normal. This is especially true of children. These cases should receive more careful bacteriological and histological examination. By the application of proper bacteriological methods and a careful histological study *Bacillus influenzæ* may be found to play a more important part in acute cerebral conditions than is generally thought; and some of the now obscure conditions, especially in children, may be due to the presence of this organism.

During the past year I have made bacteriological examinations of the central nervous system of several children, employing media on which *Bacillus influenzæ* grows best. These bacteriological examinations were made on patients who showed acute cerebral symptoms during life and in whom the tissues of the central nervous system, as a rule, showed little or no gross changes. In two cases, not included in this report, *Bacillus influenzæ*, associated with other organisms, has been identified.

The two cases here reported occurred in Boston during the past eighteen months. From the meninges of one case and from the cerebrospinal fluid and circulating blood of the other *Bacillus influenzæ* was obtained in pure culture.

CASE 1.—*Acute cerebrospinal meningitis with extensive intrapial hemorrhages and small areas of acute encephalitis. Death on the fourth day of the disease.*

Clinical History.—The patient was a male child 6 months old who had been bottle-fed, and always had been sickly. The present illness began rather suddenly three days before admission to the hospital of the Massachusetts Infants' Asylum. The child was restless and refused food. On the second day of the illness cerebral symptoms developed and increased in severity until death, a few hours after entering the hospital.

Extract from the Autopsy Protocol (H-10-174).—Body of a poorly developed, poorly nourished male child. The external orifices are normal. The mucous membranes and thoracic and abdominal muscles are very pale. The axillary and inguinal lymph-nodes are not hypertrophied.

Peritoneal Cavity, Pleural Cavities and Pericardial Cavity: Normal.

Heart: Weight 19 gm. It is very pale.

Lungs: Irregularly distributed over the pleural surfaces of both lungs are a number of small, fairly sharply outlined, bright red, firm areas, which extend a short distance into the underlying lung tissue. There are a number of similar areas scattered throughout the parenchyma of both lungs. The mucous membrane of the bronchi is deeply injected.

Spleen: Weight 8 gm. Dark red and firm. The germinal centers are barely visible.

Gastro-Intestinal Tract: This shows no evidence of disease.

Pancreas: Normal.

Liver: Pale.

Gall-Bladder: Slightly distended with normal bile.

Kidneys: Weight, 30 gm. Cortex, 3 mm. Parenchyma is very pale.

Adrenals, Aorta and Genital Organs: Normal.

Organs of Neck: Tonsils are small. The mucous membrane of the pharynx, larynx and trachea is deeply congested.

Head: The external ears, scalp and calvarium are normal.

Cerebrum: The great longitudinal sinus contains a small amount of post-mortem clot and blood-stained serum. The blood-vessels of the pia are everywhere deeply injected. There are large and small, irregularly distributed, intrapial ecchymoses and hemorrhagic areas. The ecchymoses are small. The hemorrhagic areas are irregularly distributed and they vary in size and shape. They are smaller throughout the right lateral hemisphere. The left lateral hemisphere shows a large, irregularly shaped, fairly well-circumscribed area of bright red intrapial hemorrhage, 3.5 by 5 cm. This is situated in the meninges on each side of the Sylvian fissure, and extends down into the pia, covering the Sylvian fissure itself, and on to the under surface of the left parietal lobe. There are a number of smaller intrapial hemorrhagic areas over the entire left cerebral hemisphere, most numerous and extensive in its anterior half. The tips of the frontal lobes show similar areas. Some of them extend on to the mesial surface of these lobes. All of the hemorrhagic areas are elevated and bright red, and on section are seen to involve the entire thickness of the pia. The blood-vessels of the brain substance are deeply injected, but no gross hemorrhages or areas of softening are visible. The ventricles are not distended. The fluid within them is clear and is not increased in amount.

Spinal Cord: This shows marked congestion of its blood-vessels. There are no gross hemorrhages or areas of softening.

Anatomical Diagnosis.—Acute hemorrhagic meningitis; acute encephalitis; bronchopneumonia; acute pharyngitis, laryngitis and bronchitis.

Bacteriological Findings.—Cultures taken from the hemorrhagic areas in the pia and planted on agar-agar smeared with fresh human blood show a pure culture of *Bacillus influenzæ*. Cultures made from the heart's blood are sterile. The bacillus isolated from this case showed the following chief characteristics: a very small, moderately thick, Gram-negative, rod-shaped, non-motile bacillus which stains with difficulty with the ordinary stains. In warm 33⅓ per cent. carbol-fuchsin the organism stains sharply. Some of the bacilli stain more deeply at the ends. The cultures rapidly take on involution forms. Cultural character—aerobic. When first isolated, the organism grows with difficulty and

only in the presence of hemoglobin. On agar-agar smeared with fresh human blood dewdrop colonies appear in the course of twenty-four hours. These colonies as a rule remain separate. In plain bouillon to which a drop of sterile human blood has been added the organisms grow fairly well.

Histological Report.—Tissues for examination were fixed in alcohol, Zenker's fluid and 10 per cent. dilution of liquor formaldehydi. The following stains were employed: eosin and methylene blue, hematoxylin and eosin, Gram-Weigert-Mallory's connective tissue and phosphotungstic acid hematoxylin stains.[3]

The lungs show numerous small areas of acute bronchopneumonia. In these areas the capillaries are distended and the alveoli contain many red blood-corpuscles, a few polynuclear leukocytes, and a good many delicate bacilli. These bacilli morphologically correspond to *Bacillus influenzæ*. The remaining viscera are normal.

Cerebrum: Sections from the bright red areas show intrapial hemorrhages which force the tissues widely apart. In addition to the red blood-corpuscles, which predominate, there are in these hemorrhagic areas a good many polynuclear leukocytes and a few endothelial leukocytes. The leukocytes are phagocytic, containing brownish-red pigment, the remains of disintegrated red blood-corpuscles. There are also a few very delicate, poorly staining bacilli, both intracellular and extracellular. Numerous sections of the brain and spinal cord were examined. They all show marked congestion of the blood-vessels, and an occasional small vessel in the cerebrum has about it a narrow zone of perivascular hemorrhage in which an occasional polynuclear leukocyte is seen. In one section, taken from the left cerebral cortex, there is a small perivascular hemorrhagic area in which there are numerous white blood-cells, mostly polynuclear leukocytes; a small area of acute encephalitis. The spinal cord shows marked congestion of its blood-vessels but there are neither hemorrhages nor areas of acute cellular exudate.

This case is of interest because *Bacillus influenzæ* was obtained in pure culture from the meninges and on account of the intrapial hemorrhages, acute encephalitis and the perivascular hemorrhages. In some of the reported cases of general septicemia due to *Bacillus anthracis* a similar, though more diffuse, acute intrapial hemorrhagic condition has been described. But besides these cases such extensive intrapial hemorrhagic exudate as was present in this case is rarely seen in acute meningeal infections. The microscopical areas of acute encephalitis are of interest, as well as of importance. These lesions, as noted, were not visible in the gross and were found only after a careful study of the histological material. The areas of acute encephalitis in influenzal meningitis may have some bearing on some of the temporary as well as the permanent paralyses of children following acute cerebral conditions other than genuine anterior poliomyelitis. If an area of encephalitis should occur in the cerebral center for any given muscle or group of muscles, a temporary or even permanent paralysis of those muscles might result. This suggestion is borne out by observations of others. In Cohoe's review, one of the patients who recovered from an acute attack of influenzal meningitis had a permanent facial paralysis and a partial hemiplegia.

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3. I wish to thank Miss E. M. Carl for assistance in the bacteriological work and for cutting and staining the sections on which the histological report is based.

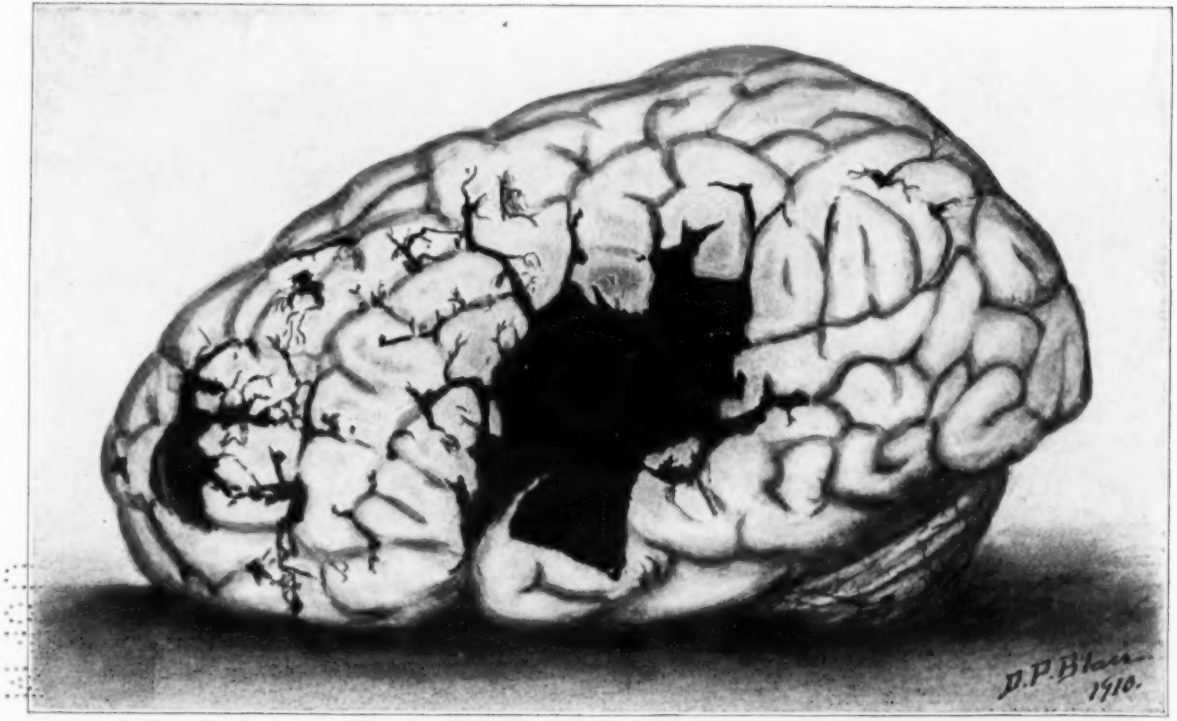

Fig. 1.—Brain of Patient 1, acute hemorrhagic meningitis, from water-color drawing.

UofM

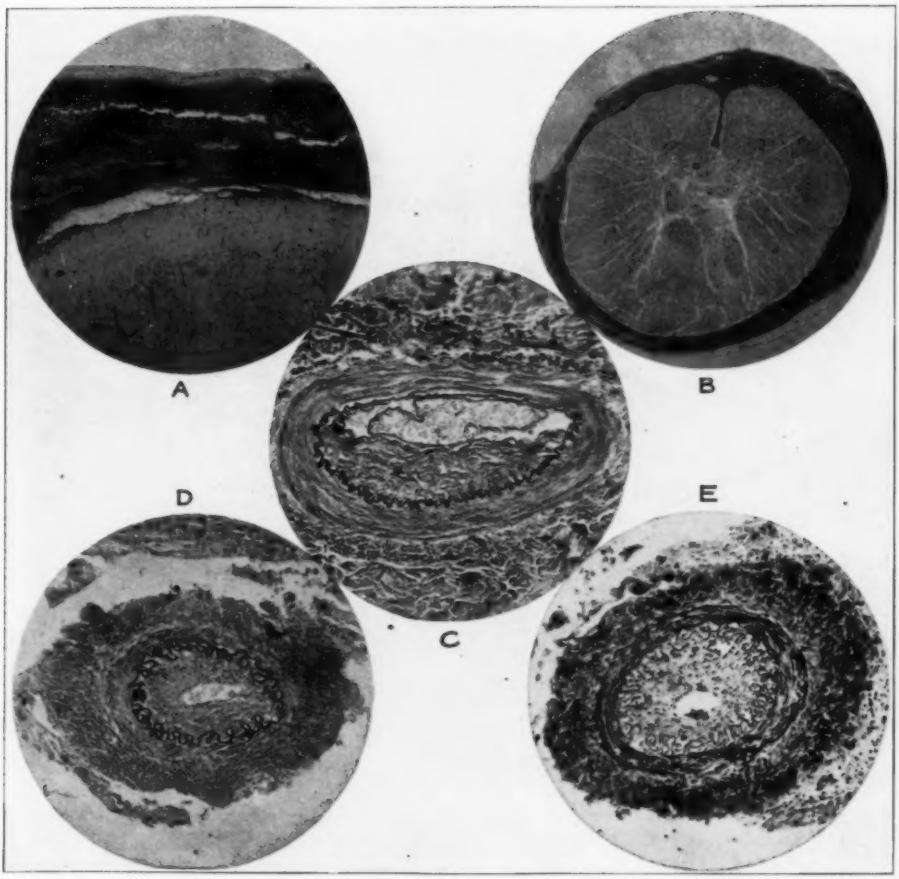

Fig. 2.—Pathologic changes in cerebrospinal meningitis due to *Bacillus influenzæ*; from microphotographs. A, transverse section through hemorrhagic area in meninges of Case 1. B, transverse section of spinal cord, Case 2. Note the marked fibrous thickening of the meninges. C, artery in pia of spinal cord near anterior commissure, Case 2. Note the localized fibrous thickening internal to internal elastic membrane. D, artery in meninges of base of brain from Case 2. There is uniform fibrous thickening of the tissues internal to the internal elastic membrane. E, artery in meninges of pons from Case 2. The lumen is replaced by connective tissue in which there are small endothelial-lined spaces containing red blood-corpuscles, a canalized thrombus.

CASE 2.—*Acute cerebrospinal meningitis and general septicemia due to Bacillus influenzæ. Death from internal hydrocephalus eighty-nine days after the onset of the disease.*

Clinical History.—The following clinical history was obtained from Dr. Wilder Tileston, the physician in charge. The patient was a girl 5 years old. She had always been a delicate child whose digestion was easily upset. The present illness began suddenly on May 17, 1909, with fever, headache and cough. At this time the throat was very red. On the fourth day after the onset of the disease a lumbar puncture was performed and cloudy fluid under considerable pressure withdrawn. The headache was severe for the first six days, then it abated and the other symptoms of meningitis became less pronounced. Fever was present throughout the entire illness, a period of eighty-nine days. The pulse was usually increased in frequency. Beginning on the seventy-third day after the onset of the disease there were occasional attacks of transitory bradycardia; the heart-rate would fall quite suddenly (but not instantaneously) from about 140 to 70 or even 50, to rise again to its former rate or more within a few minutes. During these attacks the respirations became markedly slow and labored, and there was usually unconsciousness. The attacks were not prevented by atropin given subcutaneously in full doses. There was a progressive loss of weight from 37¾ pounds at the beginning of the illness to 27¼ pounds at the time of death. Nourishment was well taken, and retained up to the thirty-third day of illness, when vomiting began and was a troublesome feature from that time on. The vomiting was of the cerebral type without retching or nausea. The bowels were constipated throughout the disease. There was incontinence of urine in the last few days. Pain in the back of the neck and in the legs was complained of at times. A complete left-sided hemiplegia appeared on the forty-fourth day of illness. This persisted with some improvement until death. Ankle-clonus (now on one side, now on both) was noted at various times, both before and after the hemiplegia. Babinski's phenomenon was present only once, on the forty-eighth day; this was on the left side. Kernig's sign was present in the first days of the disease, but not very marked. During the last few weeks of life the pupils were widely dilated, but reacted to light. Strabismus was present only toward the end and was due to independent movements of the eyes, not to paralysis. The pupils were equal. Toward the close they showed frequent alterations in size, becoming greatly contracted for short periods, even after the administration of atropin.

The heart was negative except for an occasional systolic murmur at the apex and at the base.

The spleen was only once plainly palpable.

The liver was not enlarged.

There was a marked hypersecretion of mucus in the mouth.

Urine.—During the latter part of the course of the disease there was often a heavy chalky deposit in the freshly passed urine, consisting of calcium phosphate. The urine at this time was alkaline. There was a very slight trace of albumin and an occasional cast.

Blood.—There was a leukocytosis: May 20, 18,000; May 22, 34,000; May 27, 28,000; May 31, 20,000; June 2, 16,000. A marked pallor developed in the latter part of the illness.

Treatment.—Early in the illness an attempt was made to influence the meningeal inflammation by the use of hexamethylenamin and of Flexner's antimeningococcus serum. Neither of these was of real benefit. Bromids per rectum proved useful in controlling the vomiting. An autogenous vaccine was prepared from a pure culture of the influenza bacillus obtained from the cerebrospinal fluid. Three injections were made, June 10, 13 and 19; dose, 30,000,000 to 50,000,000. They seemed to have no effect on the disease. The organisms for making the vaccine were grown in large bottom flasks. In these flasks was placed sufficient blood-bouillon to make a medium 2 cm. thick. By this means a large surface of the medium was in contact with the oxygen of the air.

Bacteriological Report.—The fluid obtained from the lumbar puncture made by Dr. Wentworth on the fourth day of the disease was turbid, and contained many leukocytes, mostly polynuclears, and a few delicate, Gram-negative, intracellular and extracellular bacilli. The sediment obtained from centrifugalizing this turbid fluid was smeared on the surface of agar-agar plates streaked with fresh human blood. From these smears a pure culture of *Bacillus influenzæ* was obtained. Two weeks after the beginning of the illness, during which time the patient ran a septic temperature, a blood culture was made. Ten c.c. of blood were taken from one of the veins at the elbow. Plates poured at this time averaged eight colonies of a pure culture of *Bacillus influenzæ* to the plate.

The organism isolated from the cerebrospinal fluid and the circulating blood of this case corresponded in every way with the one obtained from Case 1.

Extract from the Protocol (H-09-456).—Dr. Haythorn. Body of a fairly well-developed, emaciated female child, 110 cm. long. Over the entire body, with the exception of the palms of the hands and the ankles, there is a fine, dry desquamation of the skin. The axillary and inguinal lymph-glands are barely palpable. The eyes are hollow. Color is extremely pale. Lips and mucous membranes are very pale. Mouth and nose are free from discharge. Pupils are unequal; left 6 mm., right 7 mm. in diameter. Muscles of the thorax and abdomen are very pale.

Peritoneal Cavity: The surfaces are moist, smooth and glistening. The mesenteric lymph-nodes are somewhat hypertrophied; the largest one measures 1.5 cm. in diameter. They are firm and very pale.

Pleural Cavities: Surfaces normal.

Pericardial Cavity. Surfaces normal. The cavity contains 9 c.c. of clear, straw-colored fluid. Pulmonary artery opened *in situ* contains semifluid blood.

Heart: Weight 75 gm. Endocardium normal. Near the attachment of the aortic cusp of the mitral valve and on its ventricular surface there are two small, yellowish pin-point areas of thickening. On the aortic surface of the upper portion of the right coronary cusp there is a similar lesion. The heart muscle is uniformly pale and firm. Coronary arteries normal. Foramen ovale closed.

Lungs: Pleural surface normal. Parenchyma is pale and crepitant throughout. Both lungs show slight edema. There are no visible or palpable areas of consolidation.

Spleen: Weight, 35 gm. It is rather soft. The cut surface is reddish purple. Malpighian bodies prominent. Considerable blood adheres to the knife on scraping.

Liver: Weight 642 gm. Surface smooth. Anatomical markings are fairly distinct. Bile-passages normal.

Kidneys: Combined weight 132 gm. Capsule strips easily, leaving a smooth, pale surface. Cortex averages 6 to 8 mm. in thickness and is very pale. The ureters are slightly distended in their lower thirds.

Adrenals, Aorta, Genital Organs and Pancreas: Normal.

Gastro-Intestinal Tract: There is no evidence of disease. Peyer's patches and solitary follicles are not prominent.

Organs of Neck: The tongue is clean and pale. Tonsils slightly hypertrophied; they show no acute exudation. Lymphatic glands of neck are not enlarged. Thyroid and larynx normal. Thymus weighs 6 gm.; is pale and rather soft.

Head: External ears are free from discharge. Scalp and calvarium are normal. The great longitudinal sinus contains very little blood. Dural vessels are greatly flattened. The brain is exceedingly tense and bulges through the incised dura. Pial vessels are moderately injected. The convolutions of the hemispheres are broad and flat, and the sulci are shallow. There are a number of irregularly distributed, fairly sharply outlined, pale, brownish-yellow areas of thickening of the pia. These areas are larger along the course of the large blood-vessels. The largest areas of thickening are situated over the precentral convolutions and along the fissures of Sylvius. The anatomical markings of the base of the brain, pons and medulla oblongata are obscured by a grayish, tough,

fibrous thickening of the meninges, which binds the pia to the overlying tissue. This marked thickening of the meninges of the base of the brain begins anteriorly in the region of the optic commissure, extends backward along the crura over the infundibulum and corpora albicantia to the pons, surrounds the medulla and extends upward over the anterior portion of the cerebellum. The cerebellar hemispheres are firmly bound together by dense fibrous connective tissue. The ventricles are distended; the lateral ventricles contain 250 c.c. of clear, straw-colored fluid which is under great pressure. When this fluid is drained away through an opening made at the base of the brain, the dome of the cerebrum is flattened and the ventricles are collapsed. The circumference of the left lateral ventricle in its mid-portion is 12 cm. The average thickness of the overlying brain substance is 1.5 cm.

Spinal Cord: The pia of the spinal cord is greatly thickened, most markedly on one side. It is tough and of a yellowish-white color. This pial thickening is most pronounced in the cervical region, extends a short distance along the posterior nerve-roots, and thins out in the lower portion of the cord. The sinuses at the base of the brain contain a small amount of post-mortem clot.

Middle Ears: Normal.

Anatomical Diagnosis.—Chronic cerebrospinal meningitis; internal hydrocephalus; chronic endocarditis—mitral and aortic valves.

Bacteriological Report.—Cultures were made at the autopsy on media most favorable to the growth of *Bacillus influenzæ*. These cultures were taken from the heart's blood, liver, kidney and spleen, meninges of the brain and cord, several areas in the cerebral tissue, and from the cerebrospinal fluid. They were all negative for the influenza bacillus.

Histological Report.—Tissue for examination was fixed in Zenker's fluid, 10 per cent. dilution of liquor formaldehydi and alcohol 95 per cent., and stained by means of eosin and methylene-blue, Gram-Weigert and Mallory's connective tissue stain and Mallory's phosphotungstic acid hematoxylin, fat stain and Verhoff's elastic tissue stain.

Lungs: There are a few very small areas of acute inflammatory reaction. No organisms resembling *Bacillus influenzæ* are present.

Kidneys, Liver and Heart: These show a moderate amount of intracellular fat. The remaining organs are unimportant.

Spinal Cord: Histologically the meninges of the spinal cord are greatly thickened by connective tissue which is infiltrated with lymphocytes. This thickening is most marked throughout one side. Peripherally the meninges of the cord show numerous newly formed blood-vessels; a fairly active process of organization. The infiltrating cells are plasma cells and large and small lymphocytes. Besides the thickening and cellular infiltration of the meninges of the cord there are lesions of certain of the pial blood-vessels. Some of the larger arteries show focal or diffuse areas of thickening of the intima. This intimal thickening is most marked in the arteries that run along the anterior commissure and is due to a dense connective tissue internal to the elastic membrane. The arteries showing these lesions have their lumina somewhat infringed on but none examined showed complete occlusion.

Cerebrum: The thickened areas of the meninges of the brain show the same general picture as is seen in the thickened areas in the pia of the cord. The blood-vessels in these areas of thickening show lesions similar to those in the cord. One of the small arteries at the left side of the base of the brain is almost obliterated by fibrous tissue internal to the internal elastic membrane. The lumen of one of the smaller arteries in the pia covering the pons is replaced by dense fibrous tissue in which there are several small openings lined with endothelial cells. Some of these openings are filled with red blood-corpuscles. None of the sections examined showed lesions of the blood-vessels of the brain substance itself.

The connective tissue thickening in the meninges of the cord and brain is due to the organization of an exudate. The lesions in the blood-vessels most

probably have resulted from one of three changes: first, they may be organized thrombi which have been covered by the endothelial cells lining the blood-vessels; second, they may have resulted from a fibrosis following degenerations of the type seen in arteriosclerotic processes; third, some of them may be due to changes following exudation beneath the endothelial lining of the blood-vessels. Of the three causes suggested as an explanation of the pathological changes in the blood-vessels, numbers one and three are the most probable. The lesion in the artery whose lumen has been replaced by connective tissue in which there are small spaces lined with endothelial cells and filled with red blood-corpuscles, can most easily be explained as the result of the canalization of a thrombus. Thrombi in the vessels of the central nervous system have been described in influenzal meningitis. The organization of a small thrombus or a subendothelial exudate would explain the lesion in those vessels that show increase in connective tissue which is limited to a part of the vessel wall. Subendothelial exudates occur in meningitis due to certain organisms and in the smaller blood-vessels of animals that have been injected with *Bacillus mallei* or its toxin.

The important points in this case are the cultivation of the influenza bacillus from the circulating blood and the cerebrospinal fluid; the prolonged course of the illness; the development of internal hydrocephalus and hemiplegia. The hydrocephalus may have resulted from obstruction of the foramen of Magendie following the organization of meningeal or ependymal exudate. To the hydrocephalus may be attributed the pupillary signs, the attacks of unconsciousness, with slowing of the pulse and respiration, and vomiting.

The acute meningitis in this case probably followed involvement of the upper air passages, as the earliest signs of infection were noted in this location. It could not be determined whether or not the intracranial infection occurred as a direct extension from the nasopharynx or its accessory sinuses, the middle ears, mastoid cells, or by way of the circulation. There was neither clinical nor post-mortem evidence of infection of the middle ears, mastoid cells, antra of Highmore or basal sinuses.

The important points illustrated by these two cases are the following:

1. The influenza bacillus may produce a meningitis in which there are extensive intrapial hemorrhages.

2. In influenzal meningitis there may be an acute inflammatory reaction about the blood-vessels in the brain substance. These inflammatory changes may be related to some of the permanent lesions of the central nervous system following some of the acute illnessess associated with cerebral symptoms.

3. Bacteriemia may develop in the course of influenza.

4. The organization of an acute exudate in influenzal meningitis may, by interfering with the normal circulation of the cerebrospinal fluid, lead to internal hydrocephalus.

5. In chronic meningitis following acute influenzal meningitis the arteries of the meninges may show varying degrees of increase in connective tissue internal to the internal elastic membrane.

6. Influenzal meningitis may be followed by paralysis of varying extent.

SOME OBSERVATIONS ON HEART-BLOCK *

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The subject of heart-block has held a prominent position in recent medical literature. Certain features of the following cases of auricular-ventricular block appeal to me as deserving of record and discussion. They are taken from the records of the University Hospital and presented in this form on the recommendation of Dr. A. W. Hewlett, to whom I am indebted for many valuable suggestions.

CASE I.—*History.*—B. E. M., 28, student, was admitted May 20, 1909, complaining of dizziness and dyspnea on exertion. His family history and habits were good. Two years previously he suffered from a very severe tonsillitis followed by acute rheumatism. During the second week of his illness the heart-rate increased out of proportion to his illness, rising to 170 on sitting up. There was no pain but excessive nervousness and a small goiter developed. He improved on thyroidectin after seven months in bed, the pulse-rate dropping to 80-90 at the end of that time. This rate has persisted since then though he has had occasional attacks of "heart hurry." Two weeks previous to admission he had tonsillitis with little fever, and a week later the tachycardia returned with dizziness and dyspnea. After two days the heart-rate fell to 50, rose gradually to 90 and then suddenly to 160.

Examination.—Color good. Skin moist and warm. A small soft goiter, no thrill, no murmur, no eye signs. Slight lagging over the right upper thorax, auscultation of lungs negative. Some evidence of cardiac enlargement; a faint diastolic murmur noted in the pulmonary area. Radial pulse soft, large, and quick, with no irregularity.

Course of Disease.—Within a few hours after admission a partial heart-block was noticed with variable ratio between the auricular and ventricular rates, at one time a 2-1 rhythm persisted for a short time, but usually the ratio was 3-2. The *a-c* intervals in seconds were estimated as follows: 0.27-0.36-0.44-block, 0.26-0.36-0.40-block, etc. The shortest measured interval was 0.25 second and the longest 0.57 second. Following 1/50 gr. atropin the pulse became regular with an *a-c* interval of 0.27-0.30 second. Twenty minutes later there were five intermissions in one minute and five hours later the former arrhythmia had been resumed. The following morning 1/100 gr. atropin was given and the pulse became and remained regular.

Oct. 25, 1909: All symptoms had disappeared, the orthodiagram showed a reduction of 9 per cent. in the area of the heart shadow and there was no murmur.

Oct. 19, 1910: The patient returned with an afternoon temperature, a chronic cough and definite signs on the left upper chest behind. No tubercle bacilli were found. He now complained of intermissions in the pulse associated with a thump in the pericardiac region causing a cough. These were due to ventricular extrasystoles. The pulse-rate ranged from 80 to 100 per minute.

The heart-block in this case may be ascribed either to nervous influences or to the infection, both of which are commonly recognized as

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causes of dissociation. It is to be noted, however, that the irregularity followed a period of rapid pulse-rate which in itself may lead to partial heart-block as has been shown by Erlanger and Hirschfelder.[1]

The prompt improvement under the administration of atropin is convincing proof of the presence of some vagus effect. The action of the drug was not the usual one, however, as may be seen from the following:

Date	Time	Auricular Rate	Rhythm
5/20/09	At entrance	110	2-1 and 3-2
5/21/09	Before atropin	110	3-2
5/21/09	2 hrs. after atropin	95	Regular or occasional block
5/21/09	5 hrs. after atropin	90	4-3
5/22/09		82	Occasional block
5/22/09		72	Regular

The atropin produced a disappearance of the block with an improvement in the transmission time but the auricular rate has fallen rather than increased as is the usual effect. A similar experience in a case of partial block is recorded by Griffin and Cohn.[2]

CASE 2.—*History.*—S. M. B., April 12, 1910, was admitted to the otological clinic for the radical mastoid operation. Except for chronic alcoholism his previous history was negative. On April 18, operation was deferred because of delirium tremens.

Operation.—On May 9 patient was operated on under ether anesthesia. The lateral sinus was exposed, also the dura over the roof of the antrum low down.

Course of Disease.—The temperature fell to normal on the following day. On May 15 the patient complained of sharp darting pains in the head and over the face. The temperature rose to 102.2 and there was some evidence of infection in the wound. An irregular temperature persisted until the 24th. On the 23d the pulse-rate fell to 48 in the presence of a temperature of 101.2 F. and for four days the rate never rose above 56. A neurological examination on this date showed nothing. On May 26 it was noted that the pulse was irregular as well as infrequent and a tracing was taken showing an incomplete block with a 3-2 and 4-3 rhythm. The range of the *a-c* intervals was 0.27-0.42 second.

Before the action of atropin or mechanical stimulation of the vagus could be tried the pulse became regular and remained so thereafter. Tracings taken the following day were normal with an average *a-c* interval of about 0.27 second. During the several months' residence in the hospital the arrhythmia was never again observed.

The arrhythmia in this case, as in the preceding one, was probably due to vagus influence plus infection. In the absence of neurological evidence we are scarcely justified in assuming a local meningitis, or irritation of the vagus nerve. Unfortunately we were unable to apply the atropin test before recovery although we were saved, thereby, from a

1. Erlanger and Hirshfelder: Physiology of Heart-Block in Mammals, Am. Jour. Physiol., 1906, xv, 153.

2. Griffith and Conn: Remarks on the Study of a Case Showing a Greatly Lengthened *a-c* Interval with Attacks of Partial and of Complete Heart-Block, with an Investigation of the Underlying Pathological Conditions, Quart. Jour. Med., 1910, iii, 126.

probable misinterpretation of our results as *propter hoc* instead of *post hoc* in case it had resulted favorably.

CASE 3.—*History.*—March 13, 1909, a musician, aged 54, came complaining of shortness of breath and edema. He had all the features of a chronic interstitial nephritis with cardiac failure, relative murmurs, enlarged liver, chronic emphysema and a systolic pressure of 210 mm. Hg. As his condition was urgent, he was given 1 mg. of strophanthin and its action controlled by plethysmographic records. No irregularity was noted during the short period preceding administration of the drug. Within two or three minutes after this the tracings became slow and markedly irregular, enough to give rise to considerable alarm on the part of the attendants. The patient was not aware of any change in his condition.

At 5:30 (an hour later) phlebograms were taken. At the time these could not be interpreted, but they were later and in the light of clearer tracings recognized as those of partial block with a 3 to 1 rhythm; by the 17th tracings were obtained which were recognized as those of a partial heart-block. On the 20th 1/100 gr. atropin was given without recognizable influence on the arrhythmia. Mechanical and thermic stimuli produced no definite change. On March 22 digitalis was resumed in doses of 80 drops of the tincture per day for five days. The block still continued to come and go. It did not seem to be aggravated by digitalis.

The *a-c* interval was carefully estimated in a considerable number of tracings. The following are the averages for different rhythms:

During regular rhythm	.17-.22 sec. average .20
Occasional block	.13-.22 up to .35-block
3-2 rhythm	.13-.24 block
2-1 rhythm	.17-block

It is worthy of note that the shortest *a-c* interval (following a block) is considerably shorter than the usually accepted normal interval and that the interval just preceding the blocked stimulus shows comparatively little increase over the normal.

James MacKenzie[3] first reported a partial heart-block after giving members of the digitalis group, and this was later confirmed by numerous observers. We believe this case unique in the suddenness of the onset.

The production of partial heart-block by digitalis is usually ascribed to the stimulation of the vagus inhibitory mechanism, especially where an abnormally long *a-c* interval previously existed (MacKenzie[4]). Cushny[5] suggests that direct action on the conductivity of the bundle of His may be an important factor since in animals a complete block induced by digitalis is often refractory to large doses of atropin. In partial block the vagus action in man has been shown to persist by the fact that block may be induced in some cases by vagus compression or even swal-

3. MacKenzie: Diseases of the Heart, London, 1908, p. 180.

4. MacKenzie: New Methods of Studying the Heart, Brit. Med. Jour., 1905, ii, 587, 702, 759; Clinical Methods of Recognizing Heart-Block, Brit. Med. Jour., 1906, ii, 1107.

5. Cushny: The Therapeutics of Digitalis and Its Allies, Am. Jour. Med. Sc., 1911, cxii, 469.

lowing. Rihl[6] and H. E. Herring[7] state that in all previously reported cases of digitalis block the auricular rate has been increased during the irregularity. The case of A. W. Hewlett[8] seems to be the only exception to this rule.

This case under discussion showed this increase in auricular rate in remarkable degree as may be seen from the following table:

Time	Auric. rate	Ventric. rate	Rhythm
At entrance—			
3/13/09	125	125	Regular
After strophanthin—			
3/13/09	162	82	2-1
3/15/09	98	98	Regular
3/17/09	120	80	3-2
3/18/09	116	82-116	Variable
3/26/09	110	110	Regular
3/27/09	120	280	3-2

It will be observed that we have here the reverse of the paradoxical action of atropin recorded in our first case, in that a drug which usually slows the auricle by vagus inhibition caused an increased auricular rate. Moreover, the degree of the block varies with the auricular rate. Nor does the exhibition of atropin alter the picture to any considerable degree. It has been suggested that the mechanical effect of the auricular stasis stimulates the sinus to more frequent stimulus production. This by its tendency to aggravate the block establishes a vicious circle which may be interrupted either by improving conduction or slowing the auricle.

From the reports of Bachman[9] it appears that, in complete block, conditions are very different, since atropin in such cases increased the auricular without influencing the ventricular rate and the digitalis bodies slowed the auricular but increased the ventricular rate, that is, the usual vagus effect is obtained with both atropin and digitalis, while the increased ventricular rate with the latter is ascribed to direct muscular action.

CASE 4.—*History.*—A. B., 72, colored, came to the hospital April 29, 1910, complaining of shortness of breath and weakness. His first illness began seventeen years ago with symptoms of a urethritis and cystitis. Three years ago, a retention developed and suprapubic drainage for eight weeks was necessary. About a month previous to his entrance to the hospital, he suddenly became unconscious as he was sitting quietly. He fell to the floor and "believes he was paralyzed." Since then he had been short of breath, had coughed and grown weaker so that finally he went to bed. There had been some pain below the left clavicle on deep breathing. The left side had been tapped and considerable fluid drawn off; the patient did not know how much.

6. Rihl: Klinischer Beitrag zur Kenntnis der Ueberleitungsstörungen von der Bildungsstätte der Ursprungsreize zum Vorhof, Deutsch. Arch. f. klin. Med., 1908, xciv, 286.

7. H. E. Hering: Verhandl. d. Congr. f. inn. Medicin, 23. Congr., 1905, p. 153.

8. Hewlett: Digitalis Heart-Block, Jour. Am. Med. Assn., 1907, xlviii, 47.

9. Bachman: Sphygmographic Study of Complete Heart-Block, THE ARCHIVES INT. MED., 1909, iv, 238.

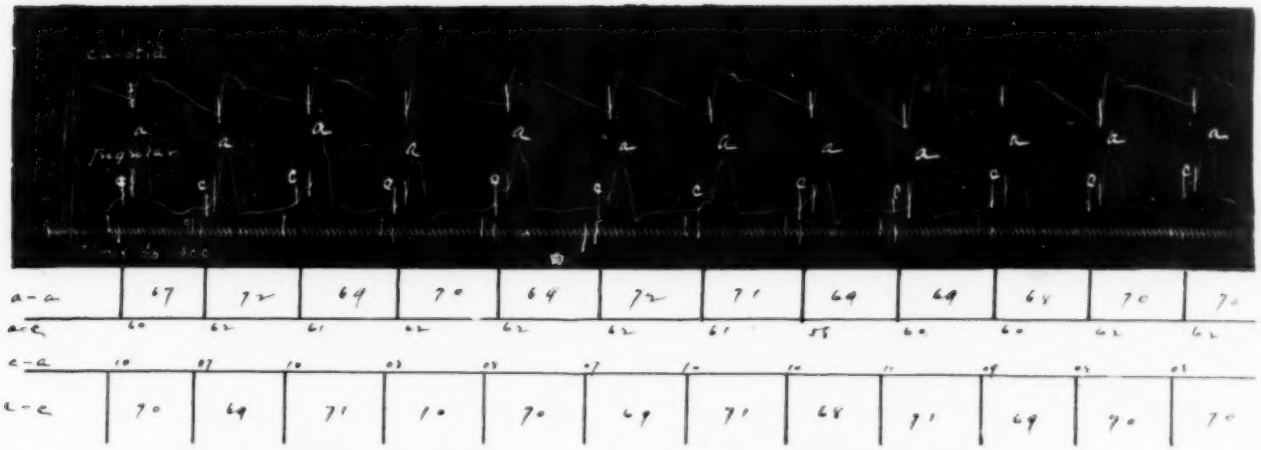


Fig. 1.—Regular rhythm; the ventricles respond to the stimulus represented by the auricular systole occurring during the preceding ventricular systole.

Fig. 2.—An occasional bloc

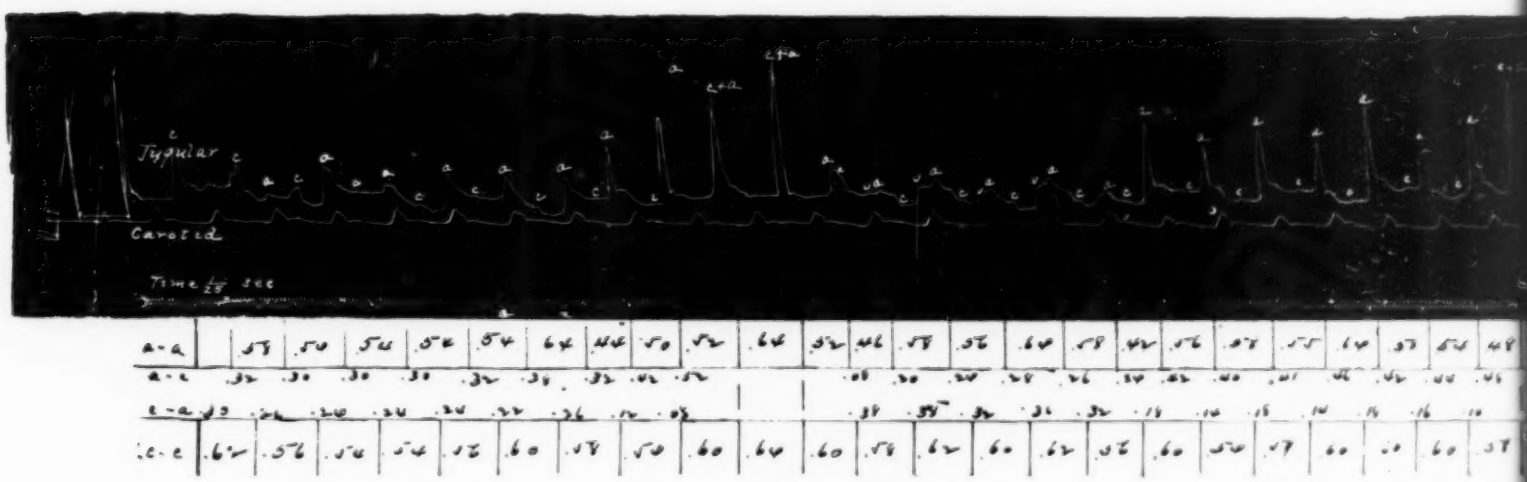


Fig. 3.—The ventricular rhythm is regular, the auricular irregular. The *a* wave is decidedly higher whenever it falls within 0.08 second before with no attempt to trace the transmissions through the bundle

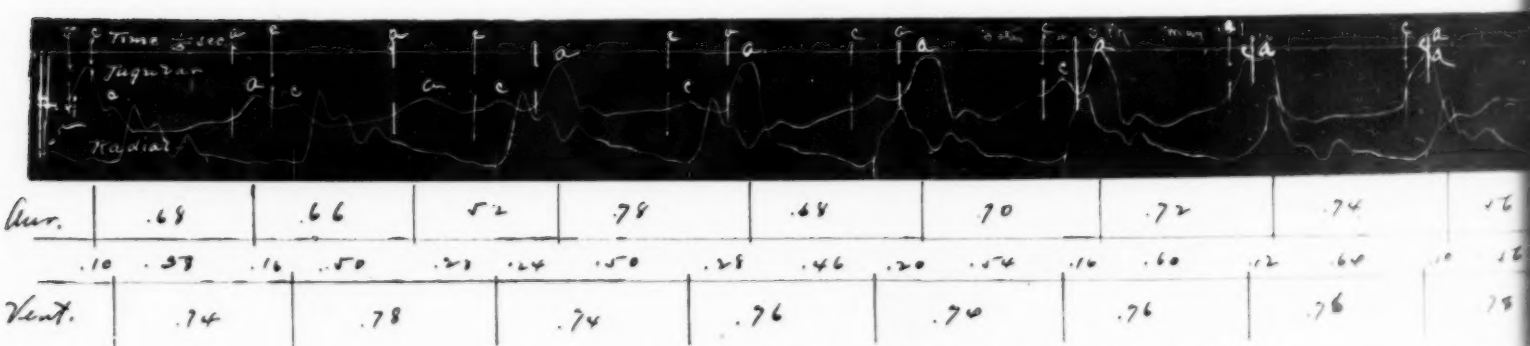
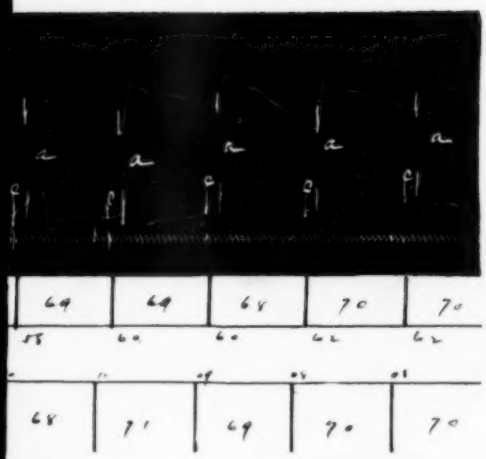
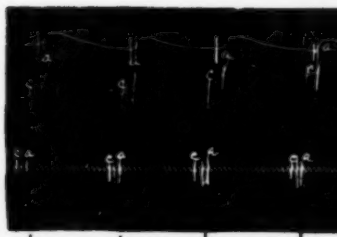


Fig. 4.—Similar to Figure 3. With the slower rate the values between which summation of a and c



auricular systole occurring during the preceding



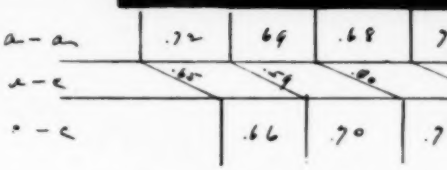
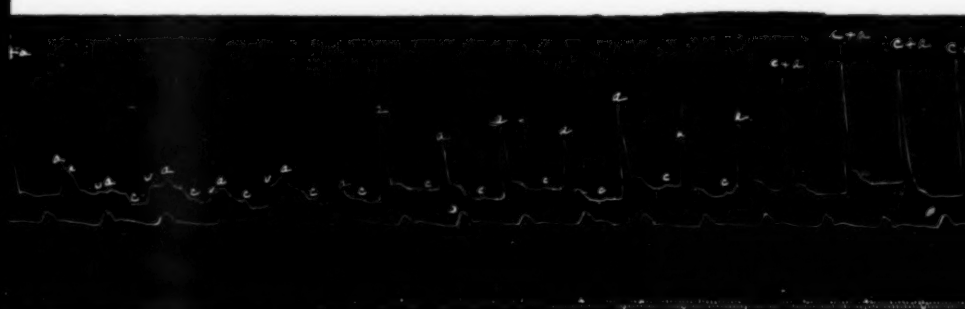
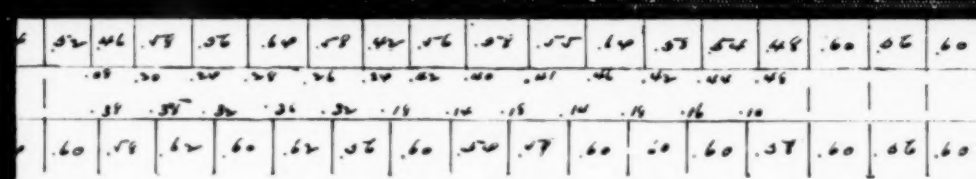
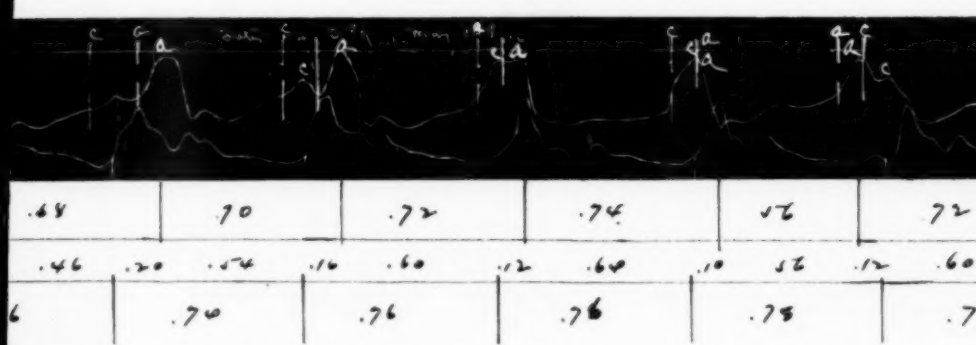


Fig. 2.—An occasional block at the end of S

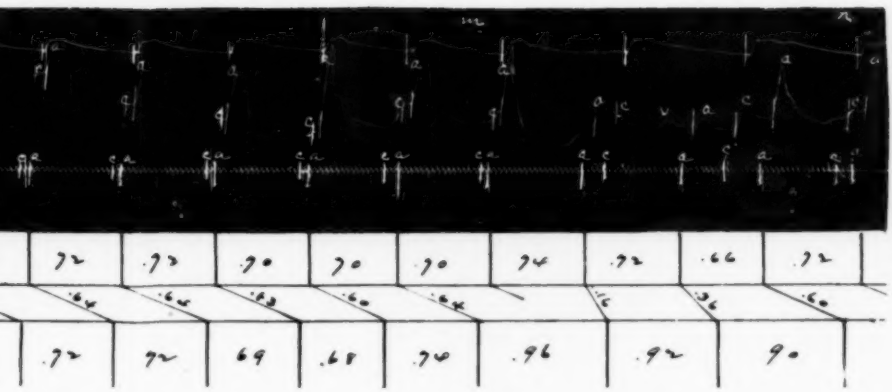




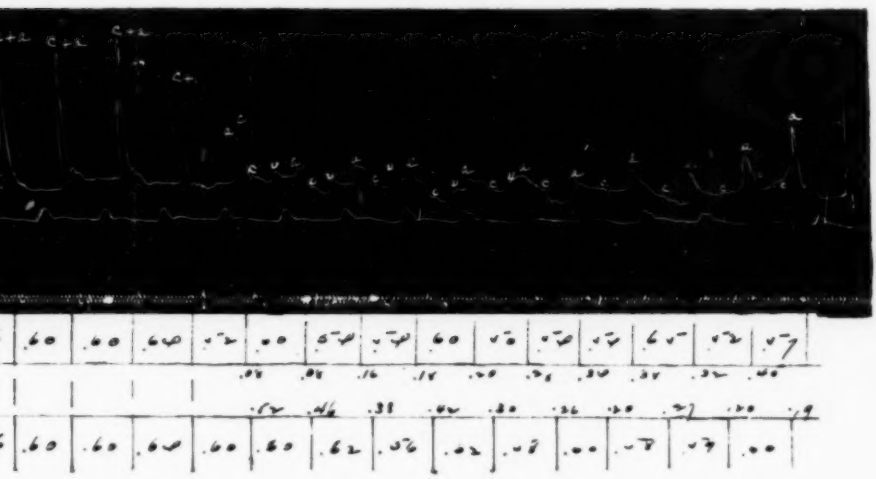
gular. The *a* wave is decidedly higher whenever it falls within 0.08 second before or 0.19 second aft
with no attempt to trace the transmissions through the bundle of His.



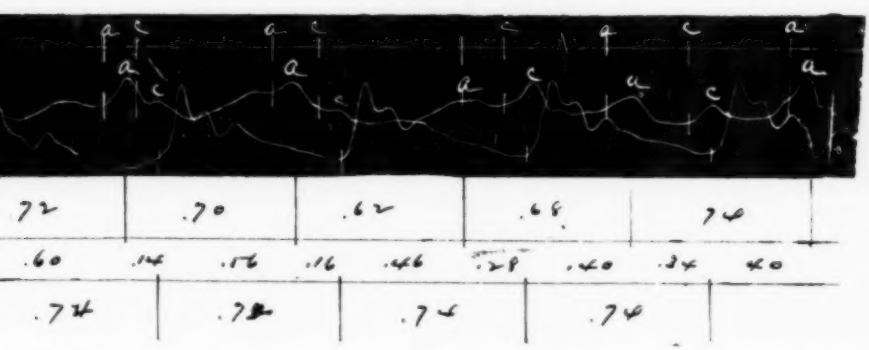
ar to Figure 3. With the slower rate the values between which summation of *a* and *c* wave occur, are so



ad of 8 mm. of regular rhythm. The diagram assumes a partial block immediately following *m*. The auricles remain regular throughout.



cond after the beginning of the *c* wave. The diagram gives the time relations



are somewhat greater.

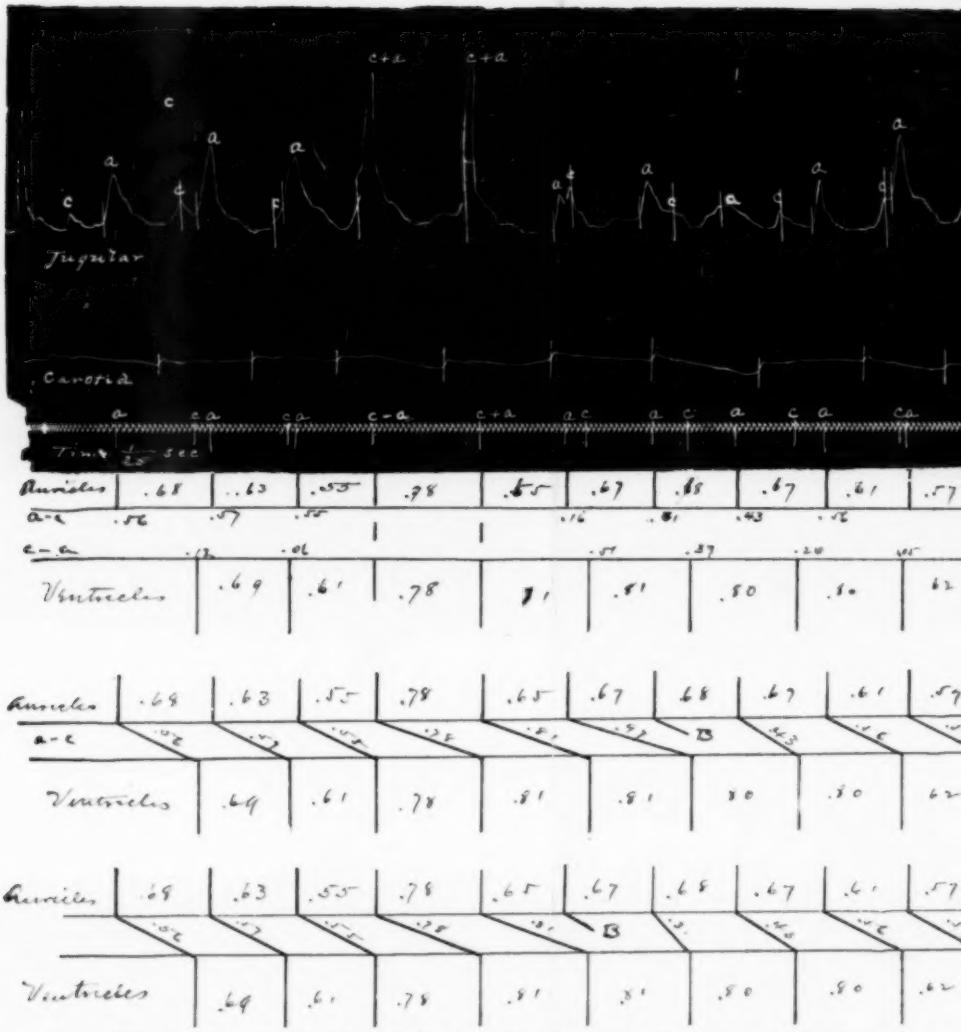
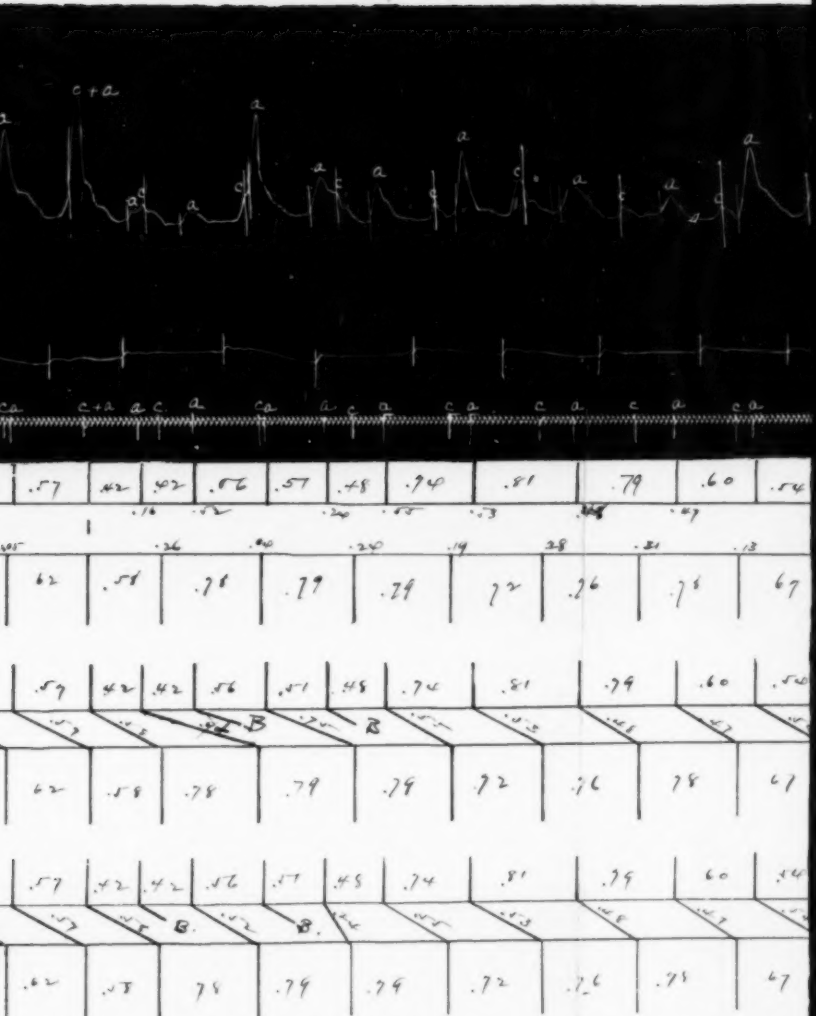
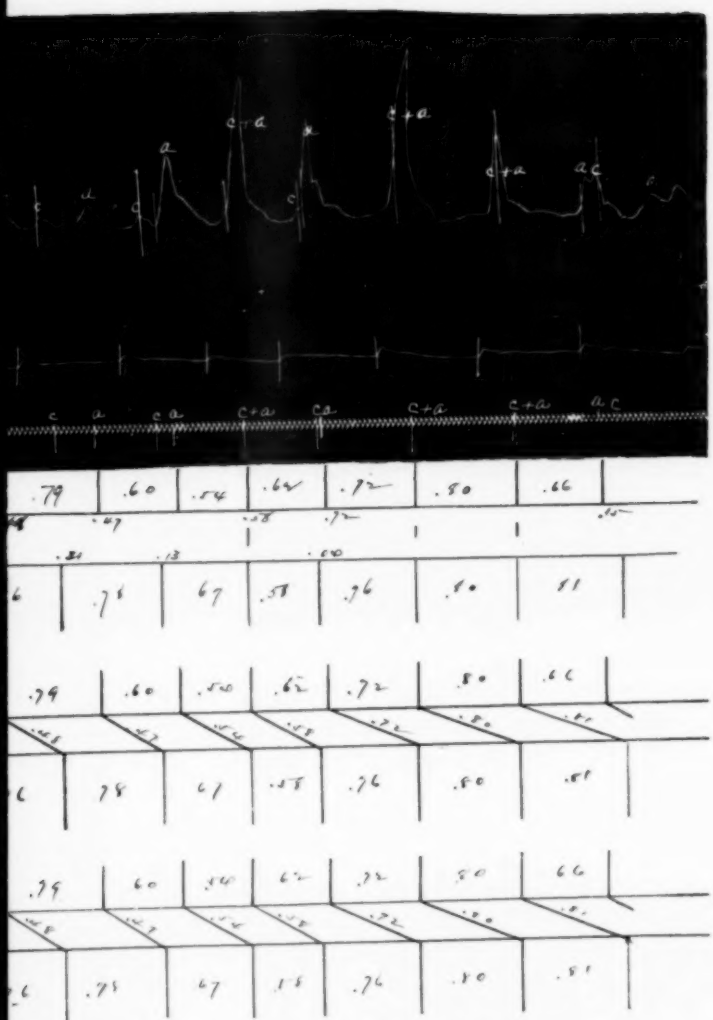


Fig. 5.—Both auricles and ventricles are irregular with fairly close relations between the *a-a*



the *a-a* and *c-c* intervals when not complicated by a block. This is best shown in the la



s is best shown in the later portion of the hypothetical diagrams.

Examination.—On entrance the bedside chart showed a temperature with a maximum of 100.4 F., pulse 92, respirations 22. The patient was orthopneic with marked Cheyne-Stokes breathing, cyanosis of the mucous membranes and full throbbing vessels. There were signs of fluid in the left pleural cavity, as high as the third rib in front with numerous râles over the remainder of both lung areas. The cardiac impulse was diffuse and might be seen as high as the manubrium and on the right side. The apex-beat could not be located by sight or touch. A slight diastolic shock was noted in the second left intercostal space. The left border of the heart dulness was lost in the dulness of the fluid. The right border was 6 cm. to right of the median line. Both sounds were distant at the apex and without murmurs. The aortic second was accentuated, also the pulmonic second. The radial was thickened, large, full and incompressible. Systolic blood-pressure was 195 mm. Hg. The liver was enlarged, firm but not tender or pulsating. There was no edema. Deep reflexes were normal. The urine showed fairly large amount of albumin, and microscopic pus. Red blood-cells numbered 4,810,000, white blood-cells 4,450; and hemoglobin was 80 per cent.

Course of Disease.—Three days later a diagnostic puncture furnished a light yellow fluid, specific gravity 1.017 with 750 white blood-cells per c.mm., nearly all of which were lymphocytes, 40 per cent. showing badly degenerating nuclei. The pleural fluid gradually decreased under depleting measures so that on the thirteenth day in the hospital the apex could be located in the fifth left intercostal space within the nipple line. The following extract is taken from a note made by Dr. Hewlett on that day: "There is a very unusual variation in the quality of the first sound, most marked at the apex but heard over other parts of the heart. At times it is loud and ringing, at others soft and muffled so that it can hardly be heard. This does not seem to depend on respiratory movements. . . . The heart is quite irregular with no relation between this and respiration. The irregularity is much less noticeable at the wrist and might easily be overlooked."

On the seventeenth day (May 5, 1910) a retention developed calling for catheterization. The urine became scanty and highly albuminous and the patient died in uremia on the twenty-eighth day (May 26, 1910).

Autopsy was refused.

The numerous polygrams from this patient fell into four classes according to the time of rhythm.

Figure 1 represents the most frequent and persistent type and is perfectly regular. It is part of a long record which remained uniform for eight minutes. In this tracing the average *c-c* interval calculated from the carotid pulse measures 0.70 second with a minimum of 0.68 second and a maximum of 0.71 second. The phlebogram shows a positive venous pulse, but the true character of the systolic elevation is not apparent until the irregular period at the end of eight minutes is studied.

This is shown in Figure 2, and represents the second type of arrythmia, viz., with the ventricles irregular and the auricles regular. The *a* and *c* waves are here easily recognized and from the portion of the tracing immediately preceding and following this irregular stage the relation of the *a* and *c* wave is easily made out. Throughout the records the *c* wave of the phlebogram slightly precedes the systolic rise on the carotid, i. e., the venous *c* wave is "protosystolic" (Bachman[10]). The irregularity cov-

10. Bachman: Interpretation of the Venous Pulse, Am. Jour. Med. Sc., 1908, cxxxvi, 674.

ers the period between the points marked *m* and *n*, including four ventricular and five auricular systoles. It will be noted that there is little change in the *a-a* intervals. The value of the third *a-a* interval is estimated at 0.66 second, although the summation of the *a* and *v* waves at this point makes its determination somewhat problematic. On the other hand the *c-c* intervals have suddenly increased from an average of 0.70 second to 0.96, 0.92 and 0.90 second respectively. These values show a difference which is very near the limit of error and do not exceed the difference between successive values elsewhere in the tracing.

Figure 3 is a reproduction of a tracing taken while the pulse-rate was considerably elevated. It represents the third type of tracing with the auricles irregular and the ventricles regular. The *c-c* interval is regular with an average of about 0.58 second corresponding to a ventricular rate of about 104. The phlebogram shows a striking alternation of high and low waves. The former occur where the period of auricular systole overlaps that of ventricular systole. Where this does not occur the excursion is comparatively slight and the waves well differentiated. In the twenty-three seconds represented in the tracing there are three more auricular than ventricular waves representing an auricular rate of about 113, as against a ventricular of 104. The *a-a* interval varies considerably (from 0.42 to 0.65). The same condition is more convincingly shown in Figure 4, taken on the previous day, when the pulse-rate was less elevated. The average *c-c* interval is 0.75 second, corresponding to a rate of eighty per minute. The average *a-a* interval is 0.68 second, equivalent to ninety per minute. Moreover, the *a-a* intervals vary from 0.52 to 0.78 without any corresponding variation in the *c-c* intervals.

Figure 5 is an example of the fourth type of tracing, in which the auricle and ventricle are both irregular. The patient had received 60 drops of tincture of digitalis during the previous thirty hours but similar tracings were obtained several days previously. Next to the regular type of tracing illustrated in Figure 1, it is the most frequent form. It will be noted that the *c-c* intervals vary from 0.61 to 0.81 second in a rhythmical manner independent of the respiratory rhythm while the *a-a* interval is subject to sudden and irregular changes.

Except in tracings of the first type it is apparent that we are dealing with some form of heart-block. Whether the block is complete or partial is not so evident.

In the light of subsequent tracings, it is easily seen that in Figure 1 we have a regular pulse with an unusually long *a-c* interval as a result of which the *a* wave falls on the *c* wave of the next preceding ventricular contraction. The transition is well marked in Figure 2, and allows of no other interpretation.

Tracings showing a similar incidence of the *a* waves on the *c* waves have been reproduced by Wenckebach,[11] Griffith and Cohn,[2] Thayer and Peabody[12] and others. Wenckebach[13] has applied the name of *Vorhof-Pfropfung* to this condition and finds the cause in the relation of the *a-c* to the *a-a* intervals. Thus it occurs whenever these become approximately equal whether from lengthening of the former in disturbed conductivity or abbreviation of the latter in tachycardia. Similar phenomena occur throughout the tracings from this patient.

It is possible in any case of auricular-ventricular dissociation in which the auricular exceeds the ventricular rate to construct a diagram showing the time relations of auricles and ventricles and by connecting judiciously selected points by slanting lines to assume the block of a number of auricular impulses equal to the difference between the two rates. Such a diagram cannot be taken as evidence of the transmission of any of the auricular stimuli to the ventricle since the relationship may be purely accidental. In a partial block we expect to find (a) the blocked impulse represented by a long interval in the carotid pulse; (b) the *a-c* interval increasing by a progressively smaller increment up to the following block; and (c) the "allorrhythmia" of Wenckebach in the radial in which the first *c-c* interval following the block is the longest of the transmitted intervals.

Applying these criteria to the diagram in Figure 2, we find the block represented by a *c-c* interval of 0.96 second, which is within reasonable errors the same as the following intervals; the increase in the *a-c* intervals following are 0.20 and 0.24 respectively (increasing increments), and the second long beat is approximately equal to the first and third. Two interpretations are here possible, viz., the block is partial and the *c-c* intervals are so nearly equal by the accidental increase of the *a-c* interval, just sufficient to produce this, or the block is complete and the ventricles have taken an automatic regular rhythm.

A somewhat similar tracing showing only two long radial pulse periods was reproduced by Joachim[14] and interpreted by the former hypothesis. Estimated from these tracings as reproduced the longest *a-c* interval is about one second while the preceding intervals are not much above the normal. Both Wenckebach[11] and Rihl[6] have questioned this interpretation and published similar instances as showing automatic ventricular contraction.

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11. Wenckebach: Beiträge zur Kenntnis der menschlichen Herztätigkeit, Arch. f. Anat. u. Physiol., 1908, Abtlg., Supplement Band 53.

12. Thayer and Peabody: A Study of Two Cases of Adams-Stokes Syndrome with Heart-Block, The Archives Int. Med., 1911, vii, 289.

13. Wenckeback: Ueber eine kritische Frequentz des Herzen bei paroxysmaler Tachycardie, Deutsch. Arch. f. klin. Med., 1910, ci, 402.

14. Joachim: Ein atypischer Fall von Störung der Reizleitung in Herzmuskel, Berl. klin. Wchnschr., 1908, xlv, 911.

Gibson and Cohn[2] report a somewhat similar case with alternative diagnosis, selecting as most probable the one assuming an *a-c* interval exceeding one second. Thayer and Peabody's[12] tracings are somewhat similar and are interpreted as due to automatic ventricular contraction.

In the case under consideration the indicated *a-c* interval of 0.90 second is not greater than occurs elsewhere where no other interpretation is possible, while an automatic rate of sixty-six per minute, which is equivalent to the rate of the long periods, is exceptionally high except under toxic doses of digitalis (Cushny[5]). The tracings of Hewlett and Barringer[15] are interpreted as such effects.

The third type of tracings with irregular auricle and apparently regular ventricle is still more involved. In Figure 3, there is absolutely no indication in the carotid of the location of the blocked stimuli. The *a-c* interval fluctuates although tending to increase to an uncertain limit. Where an *a-c* interval is shorter, however, than its predecessor, it is found to correspond to a longer *a-a* interval, possibly because the His bundle has had the longer time to recover. The contrary is also found. It seems improbable that these two factors should be so perfectly balanced as to leave no evidence of the auricular irregularity in the carotid tracing. The difficulty of recognizing the blocked auricular impulse is not removed by a study of the values of the *a-c* intervals since such short intervals as 0.08 second shown in the diagram are quite incompatible with the interval of 0.61 second during the regular periods (see Fig. 1). The inference is that the ventricle in such cases responds to the stimulus of the next preceding beat. But where the series of *a-c* readings is 0.08, 0.08, 0.16, 0.18, 0.20, 0.28, 0.34, 0.38, as occurs in the latter portion of Figure 3, there is no good indication for selecting any stimulus as the one that is blocked. The alternative of a complete block with an independent regular rhythm is very attractive in this connection, except for the unusually high frequency of the automatic ventricular rates of 113 per minute which it implies. With the exception of the case reported by Hewlett and Barringer[15] the rate of sixty-six in a case of complete heart-block reported by Windle[16] is the highest which has come to our notice.

In connection with a tracing showing similar rhythmical variations in the size of the auricular wave, Wenckebach[11] has observed a variation in the intensity and quality of the heart sounds in every way similar to that noted by Dr. Hewlett in the history and ascribes the *Vorhof-Pfropfung* above described as the cause.

In Figure 5 the difficulty of identifying the blocked stimulus is nearly as great. There is, however, an added irregularity of the carotid which reflects more or less perfectly the irregularity of the auricle plus

15. Hewlett and Barringer: Effect of Digitalis on the Ventricular Rate in Man, THE ARCHIVES INT. MED., 1910, v, 1.

16. Windle: Permanent Complete Heart-Block, Heart, 1910, ii, 102.

an occasional block. Two alternative diagrams are given as plausible interpretations of this tracing although others are possible. The relationship between the two rhythms is too close to allow of interpretation as complete block—it would be inconceivable that two independent rhythms should show similar fluctuations for any considerable length of time. The long periods of regular rhythm are also incompatible with an independent ventricular rhythm.

SUMMARY

1. Two cases of partial heart-block due to vagus stimulation or to acute infections or to a combination of these.

2. One case of partial block following the injection of 0.001 gm. of strophanthin.

3. One case of partial block apparently cured by the use of atropin. Two cases in which such injections produced no notable effect on the block.

4. When the block followed strophanthin the auricular rate was increased and when the block disappeared after atropin the auricular rate was lessened.

5. The last case showed partial block with the following peculiarities:

A. Long periods of regular rhythm during which the auricles contracted during ventricular systole. In such cases the ventricles responded to the stimuli coming from the previous auricular contractions, the *a-c* interval being about 0.60 second.

B. Repeated *a-c* intervals of more than 0.80 second.

C. Auricular irregularity with such relations between the *a-c* intervals and the *a-c* increments due to fatigue that the ventricles showed no evidence of the auricular irregularity.

319 Glen Avenue.

FRACTURE OF CERVICAL VERTEBRÆ, RESULTING IN HYPOTONIA AND HYPOTHERMIA*

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The Injury.—On the evening of Jan. 28, 1911, a man was seen to fall from a subway station platform to the tracks, about 4 feet below, on his back. He was lifted to a seat on the platform and a policeman who was notified called an ambulance. On the arrival of the ambulance surgeon, about fifteen minutes later, the man was found to be confused, and to be weak but not powerless in his legs. The knee-jerks were present and his arms and trunk showed ample strength. He could not walk and there was a smell of liquor on his breath, so he was taken to the police station, charged with intoxication.

The next morning the officer in charge found the man unable to stand, though less confused and able to give a fair account of himself. The ambulance surgeon was called again and found the reflexes at the knees weaker but still present, and an increasing disability in the legs. The man could use his arms and trunk to some extent. He was brought to the prison ward at Bellevue Hospital, charged with intoxication but with a diagnosis of transverse myelitis or possible fracture or dislocation of a cervical vertebra.

On admission on January 29, the patient was semi-conscious, roused later, and became somewhat noisy. His eyes were stupid and staring. He gave a connected story of himself but had forgotten having gone down into the subway station. He remembered walking along the street and feeling dizzy, and then coming to himself in the station house.

History.—He gave a family history as follows, and it was corroborated by his wife and his employer:

Father is living and well; occasionally subject to dizzy spells. Mother died at 28 of tuberculosis. There was one brother, who died at 44 of softening of the brain. There has been tuberculosis among aunts and uncles.

He says he has never been sick except for an attack of gonorrhea fifteen years ago; has always been in vigorous health and a hard worker, never took medicine or was under a doctor's care. He is a porter by occupation, a negro, 38 years old, married and has no children. He is accustomed to use beer moderately and gin occasionally in his home or at the house of friends. He is not a user of tobacco. Uses tea and coffe in moderation.

Examination (January 30).—An unusually well-nourished and well-developed negro, with a well-shaped head and intelligent face. Nothing abnormal was found, except a distended bladder, evidence of injury at the back of the neck and extensive motor and sensory paralysis. There was a temperature of 97.8, pulse 58, respiration of 20 in the minute, pulse small and easily compressible. There was incontinence of feces and retention of urine, no difficulty in swallowing, breathing of diaphragmatic type.

There was no interference with any of the special sense organs, but there was a persistent and equal contraction of the pupils, so extreme that but slight response to light could be elicited.

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*Report was read at the meeting of the American Society for Clinical Investigation, May 8, 1911.

*This case is reported from my term of service as physician to the alcoholic and prison wards of Bellevue Hospital, and the clinical observations were corroborated by Dr. V. H. Norrie, visiting physician to Bellevue Hospital.

From the region of the fifth to the seventh cervical spines there was moderate tenderness with acute pain on pressure where the sixth spine should have been felt. Owing to the heavy musculature, proof of mobility or crepitus on palpation could not be obtained. There was least discomfort when the head was in extension. There was moderate muscular spasm of the posterior neck muscles. There was little subjective discomfort at the sight of injury. The skin was intact. Without going into the details of the paralysis, it suffices to state that there was a loss of muscular sensory and reflex power below the level of the distribution of the sixth cervical nerve roots.

There was a sharp line of loss of power and sensation, and reflexes were abolished below this level, roughly complete paralysis below the clavicles and of the arm muscles, except the supinators and deltoid.

There was no zone of hyperesthesia.

Lumbar puncture showed bloody fluid under no tension.

X-ray taken January 31 showed fracture of the posterior arch of the sixth cervical vertebra.

Treatment.—Surgical advice obtained was unfavorable to operative interference. Treatment consisted of attention to the bladder and general nursing care. On the nights of February 1 and 2 atropin, gr. 1/100, was given hypodermically on four occasions to assist the respiration which became suddenly labored and dyspneic.

Course and Termination.—The patient remained alert and intelligent and in but moderate discomfort. The pain in the back of the neck gradually increased from day to day. On the morning of February 3 there was a sudden increase in dyspnea. There were signs of accumulation of fluid in the lungs and the patient died of failure of respiration at 6:15 a. m.

From the time of admission for forty-eight hours the temperature ranged from 97.8 to 96.2 F. After that the temperature deep within the rectum (3 inches from the anus) was always a little over or under 90 F.

The pulse ranged from 80 to 44, the latter rate being recorded five hours before death; it was always small and compressible. The respiration ranged from 18 to 24, the rate being 26 for a few hours before death.

The blood-pressure was not taken until January 31, and it was then 88 mm. Hg. On other occasions it varied but a few millimeters from 90.

Necropsy.—The necropsy, performed at 11 a. m., February 3, by Dr. Otto Schultz, confirmed the diagnosis. There was ecchymosis in the deep muscles of the neck posteriorly. There was a complete separation of the posterior arch of the sixth cervical vertebra with an overriding of the seventh on the sixth, and a fracture without displacement of the right side of the arch of the fifth cervical vertebra where the arch leaves the body of the vertebra. There was gross evidence of injury to and slight softening of the cord at the site of the injury, i. e., between the sixth and seventh vertebræ. There was a little blood in the spinal canal. The brain and cord were removed for subsequent study. There was no evidence of edema in the lungs. Nothing was found to explain the dizziness preceding the accident.

There were no lesions found in any other organs which bear in any way on the report of the case.

I have found no report of a case of fracture of the spine in which low temperature and low blood-pressure were observed, nor have I been able to learn of such observations by personal inquiry and correspondence with surgeons who have had much experience in spinal surgery. Such hypothermia and hypotonia should follow complete severance of the cord just below the phrenic nerve origins. By such breaks in the connection between the medulary vasomotor and heat regulating centers

and so large a part of the body, all vasomotor tone and heat regulation in the body below that part should be abolished. It is a common physiological observation that section of the cord at the sixth cervical vertebra in dogs and rabbits and cats will cause an immediate fall in blood-pressure, which is only in part recovered from in these animals by resumption of vasomotor control by the subsidiary spinal and ganglionic centers below the point of section. What is less known is that Nebelthau in 1895 found, on section of the cord in rabbits between the sixth and seventh cervical vertebræ, that there was a prompt and marked fall in body temperatures and that this is due to a marked diminution of heat production and heat elimination. After section of the cord in this way he was unable to develop fever in spite of injections of erysipelas cultures of the pig. In 1881 Mendelson[1] found the same fall in temperature as a result of the effect of morphin, chloral and curare in dogs and the same failure to develop fever by the injections of pus, hay infusion, and pepsin in such animals. In both cases there is apparently an interference, in Nebelthau's[2] cases, with the path from the centers to the periphery, and in Mendelson's cases, with the activity of the centers and the ability to cause muscular contraction.

The case above reported seems to give clinical support to two important experimental observations in spite of the absence of control records. Unfortunately I cannot offer records of the temperature and blood-pressure in my case before the accident. Two clinical lessons may be drawn from this case. First, that in the injuries to the cord in the vicinity of the sixth and seventh cervical vertebræ the presence of hypothermia and hypotonia would go far to prove that there was a complete separation of the cord from the medulla, or that even if there were sensory and motor paralysis pointing to a complete transverse lesion of the cord at that level, there would be a fair inference that the separation or destruction was not complete if hypothermia and hypotonia were absent. By separation I mean functional and not necessarily anatomical. Second, that it will be well to be on our guard against the existence of complicating lesions in such cases as I have reported because it would seem quite possible that even severe inflammatory processes usually accompanied by fever might occur without the warning of a rise of temperature. It is possible that the slow heart rate in this case was a secondary result of the low temperature, for one should have expected a compensatory increase of heart rate in a patient with such a low blood-pressure and the lesion did not involve the reflex cardiac nervous mechanism at all.

120 East Sixty-Second Street.

1. Mendelson: Am. Jour. Med. Sc., 1883, new series, lxxxvi. 380.
2. Nebelthau: Ztschr. f. Biol., 1895, new series, xiii, 293.

THE RELATION BETWEEN ACUTE INFECTIOUS DISEASES AND ARTERIAL LESIONS *

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The object of this study has been to find whether, during the course of the different acute infectious diseases, any general lesion can be found in the arterial system which seems surely to be the result of the toxins of the disease or of a wide-spread distribution of the infective agent. Furthermore, if such a lesion does exist, is it of a kind that will result on healing in a permanent injury to the arterial system?

That the infective agent may lodge locally in the arterial wall has been shown by the reports of cases in which the tubercle bacilli and the spirochetes of syphilis have been found in human arteries. Wooley[1] has recently reported a case and refers to the other cases reported in which the tubercle bacilli have invaded the intima of the aorta in one or more places from the blood stream. Wright[2] and Richardson were among the first to demonstrate the *Treponema pallidum* in the wall of the aorta in syphilitic aortitis. Also, as Osler points out in his "Modern Medicine," localized acute arteritis may occur in which the invading organism can be demonstrated. Rhea[3] recently reported lesions in arteries of the meninges in a case of hydrocephalus and brain abscess, following an acute influenzal meningitis. This lesion consisted in marked connective tissue thickening of the intima, occluding more than half the vessel's lumen. In this case no organisms were found in the arterial walls, so it is not known whether these lesions were due to the actual presence of the influenza bacillus or to concentrated toxic action followed by thrombus formation and organization. Robertson[4] and Chesley describe a degeneration in the vessel walls in the spinal cord in cases of acute anterior poliomyelitis. Here again it is uncertain whether this action is due to the actual presence of some organism or to some toxin. Thus it is evident that infective agents and possibly their toxins may cause local lesions of a permanent character in arteries. The next question is whether these agents or toxins can cause a diffuse lesion. In

*From the Laboratory of the Department of Theory and Practice of Physic, Harvard University. Published with the approval of the committee as work done under a Bullard Fellowship.

1. Wooley: Bull. Johns Hopkins Hosp., 1911, xxii, 82.
2. Wright and Richardson: Boston Med. and Surg. Jour., 1909, clx, 539.
3. Rhea: Reported American Assn. Path. and Bact., 1910.
4. Robertson and Chesley: THE ARCHIVES INT. MED., 1910, vi, 233.

the literature almost all of the infectious diseases are accused of causing degenerative or proliferative changes in the aorta and other vessels. Thus Osler in his "Modern Medicine" in the chapter on arteriosclerosis considers that the acute infections form one of its etiological factors. He says that in scarlet fever, measles, diphtheria, small-pox and influenza foci of arterial degeneration occur with great frequency. In typhoid fever areas of necrosis and fatty degeneration are met in the aorta. Huchard[5] in 1891 and his school considered that the acute infectious diseases of childhood were largely responsible for the arteriosclerosis of adult life. Hofbauer[6] in 1903 reports on the development of arteriosclerosis in a boy of 17 after an attack of measles. Thayer[7] and Thayer[8] and Brush in 1904 present evidence that there is some relation between typhoid fever and alcoholism on the one hand and the development of arteriosclerosis on the other. Wiesner[9] found extensive calcification in the coronary arteries of young people following endocarditis or prolonged osteomyelitis. Wiesel[10] made extensive studies of the heart and blood vessels of young persons in typhoid fever, scarlet fever, measles, diphtheria, sepsis, pneumonia and osteomyelitis. He found in thirty out of 300 autopsies signs of arteriosclerosis in both larger and smaller vessels. The lesions in the media were similar to those found in experimental arterial disease in rabbits. Adami[11] agrees that in burns and acute infections it is common to find fine fatty streaks in the aorta. Fremont-Smith[12] considers that arterial disease is common in the young and that the media is usually primarily involved. Symnitsky[13] in 138 autopsies on people under 25 years of age who died of acute infections found sclerotic changes in the aorta in thirty-eight. If patients under 2 years of age were left out in which he found no lesions, the sclerosis in the aorta occurred in 48 per cent. of these cases.

Turning to the experimental side, there is considerable evidence in favor of the possibility of toxins or their causative agents producing arterial lesions. After injury to the aorta, Gilbert[14] and Lion in 1889 succeeded in causing aortic lesions by the injection intravenously of typhoid bacilli and a malignant bacillus isolated from a human case. Since that time several authors have published reports of the successful production of arterial lesions in rabbits by the use of different toxins

5. Huchard: Rev. gén. de clin. et de thérap., 1891, v, 637.
6. Hofbauer: Wien. klin. Wchnschr., 1903, xvi, 983.
7. Thayer: Am. Jour. Med. Sc., 1904, cxxvii, 391.
8. Thayn and Brush: Jour. Am. Med. Assn., 1904, xliii, 726.
9. Wiesner: Wien. klin. Wchnschr., 1906, xix, 725.
10. Wiesel: Wien. klin. Wchnschr, 1906, xix, 723.
11. Adami: Am. Jour. Med. Sc., 1909, cxxxviii, 485.
12. Fremont-Smith: Am. Jour. Med. Sc., 1908, cxxxv, 199.
13. Symnitsky: Ztschr. f. Heilk., Prague, 1903, xxiv, 177.
14. Gilbert and Lion: Compt. rend Soc. de biol., 1889, p. 583; Arch. de méd. expér. et d'anat. path., 1904, xvi, 73.

or bacteria. Among these the following names appear frequently: Crocq,[15] Pernice,[16] Thérèse,[17] Boinet and Romary,[18] Saltykow,[19] Klotz,[20] and Du Val.[21] Klotz finds that different bacteria act differently. Typhoid bacilli and streptococci caused fatty degeneration of the subendothelial tissue and also proliferation, while on the other hand diphtheria bacilli produced only a degenerative lesion. Du Val obtained a proliferation of the endothelium with injections of attenuated glanders bacilli. Others mention round cell infiltration in different layers of the arterial wall.

Most of the experimental work has been done on rabbits. Adler[22] says that arterial disease has been reported in the ox, horse and dog. A few of the experimenters have used guinea-pigs and other animals as well as rabbits, notably Pernice, Boinet and Romary, and Thèrése.

From the above reports on human cases and experiments it seems fair to assume that acute infectious diseases may cause some pretty general lesion throughout the arterial system, either from the diffuse action of toxins or from a wide-spread invasion of the arterial system by the infecting organism. The exact nature of these lesions in human cases and their final result has not been so well worked out. In order to throw some light on this phase of the question this study was undertaken.

Pieces of tissue from the aorta, spleen and kidney were taken at random. The tissue had been preserved in Zenker's fluid and 10 per cent. liquor formaldehydi. The Zenker's fixed material was mounted in paraffin, cut and stained with eosin and methylene blue, and Verhoeff's elastic tissue stain. The formalin fixed material was cut by the freezing microtome, and stained with Scharlach R. for fat. The Scharlach R. stained material was very carefully studied as the presence of fat droplets in cells of the arterial walls is one of the earliest signs of injury. It was thought that tissue taken at random from these three parts of the body would show as well as any tissue a general lesion to the arterial system away from the site of the active process of the acute infection.

At first, tissue from people of all ages was studied, but it was soon found that the majority of people above 25 years showed the same arterial lesions whether they died of acute infections or chronic disorders; and furthermore, that these lesions were very similar to those seen during some acute infections in young people.

15. Crocq: Arch. de méd. expér. et d'anat. path., 1894, vi, 583.
15. Pernice: Atti d. r. Accad. d. scienze med. in Palermo, 1895.
17. Thérèse: Thèse, Paris, 1893.
18. Boinet and Romary: Arch. de méd. expér. et d'anat. path., 1897, ix, 902.
19. Saltykow: Zieglers Beiträge, 1908, xliii, 147.
20. Klotz: Brit. Med. Jour., 1906, 2, 1767.
21. Du Val: Jour. Exper. Med., 1907, ix, 241.
22. Adler: Am. Jour. Med. Sc., 1908, cxxxvi, 241.

In people above 30 years the following lesions were pretty consistently present. In the arteries of the kidneys there were fat droplets in the muscle fibers of the media and occasionally in the intima. In addition there was frequently an increase in connective tissue of the intima. The spleen showed a hyaline-like change in the walls of its smaller arteries usually involving the intima and occasionally involving the media. Around the hyaline material there was no cellular reaction, and it took the fat stain rather feebly. In the muscle fibers of these and larger arteries there were fat droplets. In the media of the aorta fat droplets were present in the muscle fibers. In the intima there were thickened areas, and in these thickened areas fat. Also there was fat scattered pretty generally along the intima. At the places in the media corresponding to the thickened places in the intima the fat droplets were much more frequent in the muscle fibers suggesting a more marked degeneration of the muscle at these points. In the thickened intima endothelial cells were frequently present and around the vasa vasorum round cell infiltration in slight amount occurred.

No other lesions which could be attributed to acute toxic action were noted. In some cases marked increase in fibrous connective tissue occurred which at times replaced the muscle to considerable extent. In other cases calcareous spots were found. It seemed reasonable to assume, however, that these lesions were the result of some former process, and not due to an acute infection.

Between the ages of 30 and 65, three cases of typhoid, one of pneumonia, one of sepsis, and four of local or general peritonitis were studied as representatives of acute infections, while five cardiac cases, two of nephritis, one of cancer, one of aneurism and one cerebral case as examples of chronic non-infectious disorders. From a study of these cases it soon became evident that the lesions described above were quite generally distributed through both series, and that in order to draw any conclusions in regard to acute infections, selected cases should be studied in which chronic disorders could be practically eliminated.

For this purpose a series of fifty-six subjects under 25 years of age were studied. Most of them died from acute infectious diseases, but there were a few infants and others who died of non-infectious illnesses. there were a few infants and others who died of non-infectious illnesses. each of these fifty-six cases it was not possible to obtain tissue from all the three parts of the body which had been preserved in both fixatives. Six cases of tuberculosis were studied, one of which was that of an infant 1½ years old. The arteries in this infant were negative throughout; a fact which was noted in practically all the infants, no matter what was the cause of death. In the kidneys of the remaining five subjects there was an increase in the connective tissue of the intima of the arteries in three, and in these cases fat droplets were present in

the muscle fibers of the media. The other two cases showed apparently normal arteries in the kidney. Of these two only one was stained for fat, and that was negative. In the spleens of these five cases a hyaline degeneration of intima and media was present which took a feeble fat stain. In four of the five, fat droplets were present in the media muscle fibers. Only three aortas were preserved. They all showed a thickening of the intima. In two of these formalin tissue was preserved, and they showed fat in the intima and fat droplets throughout the muscle fibers of the media.

Two cases of typhoid fever were studied. The arteries in the kidney appeared normal except for a very rare fat droplet in the muscle fibers. In the spleen one showed a slight hyaline degeneration with no droplets of fat in the media fibers, and the other showed no hyaline degeneration and an exceedingly rare fat droplet in the media. In the aorta of both there was a slight increase in thickness of the intima with fat present and fat droplets in the muscle fibers of the media. These subjects were 21 and 24 years old, and are valuable as controls in that their renal and splenic arteries were so nearly normal.

Of four pneumonia cases, one was in an infant 10 months old which showed normal arteries throughout. Another patient was 1⅔ years old. In this case there was no aorta preserved. The renal arteries were negative and also the splenic vessels except for a slight hyalin degeneration. The other two cases showed an increase of connective tissue in the renal arteries with fat droplets in the muscle fibers. In the spleen there was hyaline degeneration which took the fat stain in both cases, and one of them also showed fat droplets in the muscle fibers. Both aortas showed an increase in the thickness of the intima with fat present and fat droplets in the muscle fibers of the intima.

Three of the ten diphtheria patients were under 2 years of age, and showed normal arteries throughout, although the spleen and aorta were only preserved in two. Of the remaining seven cases, six showed normal kidney arteries, and one showed a slight increase in connective tissue and fat droplets in the muscle fibers. This patient was 25 years old, however. In the spleen all seven cases showed hyaline degeneration which took the fat stain, and three of them showed fat droplets in the muscle fibers of the media. The material from the aorta in this series was rather scanty. Four out of five showed thickening of the intima. Five out of six showed fat in the intima and two out of six showed fat droplets in the muscle fibers of the media.

The next group of twelve is composed of septic cases such as peritonitis, osteomyelitis, endocarditis, bronchopneumonia, etc. Of these twelve, one only showed a suggestion of increased connective tissue in the kidney arteries, and two only showed fat droplets in the muscle

fibers of the arteries. Seven cases showed the usual hyaline degeneration in the splenic arteries and five did not. Only one of these twelve showed fat droplets in the muscle. Ten aortas in this group were examined, of which six showed some thickening in the intima with fat drops, while in four the intima was apparently normal. Two of the ten showed fat droplets in the muscle fibers of the media.

In two cases of measles, the subjects being under 2 years of age, the arteries were normal in all the tissues examined.

One case of acute poliomyelitis presented normal arteries. Another which was complicated with status lymphaticus showed normal renal arteries, normal splenic arteries except for slight hyaline degeneration, and in the aorta thickening of the intima with fat drops, but no fat droplets in the media.

Two cases of meningitis, one of which was a chronic influenzal meningitis, were normal throughout. The influenzal case is interesting, as it is the same case that is mentioned above in which Dr. Rhea found lesions in the meningeal vessels which strengthens the view that toxins may act locally and not in a general manner.

Three cases of bronchopneumonia in infants showed normal arteries.

Of two patients with scarlet fever, one aged 3 showed normal arteries throughout. The other showed necrosis of the whole arterial wall with fibrin formation and cellular reaction in some of the renal vessels, while the other renal vessels were apparently normal. These necrotic vessels showed fat present. In the splenic arteries there was slight hyaline change which took the fat stain but no fat droplets in the muscle fibers. The aorta appeared normal with the eosin and methylene-blue stain. There was no formalin material from which to make a fat stain.

One case of glanders in a man 25 years old showed normal amount of connective tissue in the renal arteries but fat droplets in the muscle fibers. The splenic arteries showed hyaline degeneration but no droplets in the muscle fibers. In the aorta the intima was thickened and had fat in it, and the muscle fibers of the media contained droplets which were much more marked close beneath where the intima was thickened.

Five infants under 9 months who died from such obscure causes as inanition, ileocolitis, petechial hemorrhages, etc., failed to show any lesions in the aorta or arteries of the kidney and spleen.

Five cases, one chronic nephritis, one hydrocephalus, one congestion and edema of lungs, and two cardiac cases, were used as controls. Of these five, the nephritis case alone showed a lesion of the renal vessels. This case showed connective tissue increase in the arterial wall and fat droplets in the muscle. In the spleen, two of the five showed the usual hyaline degeneration, and one of the four in which there was formaldehyd tissue showed fat droplets in the media muscle fibers. In the

aorta the intima was thickened in four cases, and these cases showed fat in the intima. These four also had fat droplets in the muscle fibers of the media. The other one showed a normal aorta.

From a study of these fifty-six subjects it is evident that the same lesions exist in their arteries as in the older subjects that died of acute or chronic diseases. Therefore, there is no general arterial lesion peculiar to the toxins of the acute infectious diseases. As no evidence of bacteria was found in any of these lesions it seems probable that these lesions, if due at all to the infectious diseases, must be the result of toxic action.

A peculiar feature in the action of toxins is showed in the scarlet fever case in which part of the renal arteries were normal, while others showed extensive necrosis. Apparently in this case the toxin had a selective action for certain of the vessels. A study of this case in detail will be reported in another communication.

The facts that practically no lesions were found in cases under 2 years of age, that the lesions differed in the different tissues, and that the arteries in the three sets of tissue were not equally affected in each case, argue against the supposition that these lesions are caused by toxins of the acute infectious diseases.

On the other hand, the frequency with which these lesions occur in certain groups of cases makes it seem very probable that there is a relation between them and the acute infectious diseases.

In considering only the acute infectious cases (infants and others), the kidney was studied in forty-six cases, in seven of which there was connective tissue increase and in eleven fat droplets in the media. Eight of the eleven cases with fat droplets were in cases of typhoid fever, tuberculosis, pneumonia and glanders. These patients, however, were all nearly 25 years old. It seems reasonable, therefore, to state that as a result of acute infections connective tissue increase in the renal arteries is not to be expected, nor is any fatty degeneration of the media probable except possibly in typhoid fever, glanders, pneumonia and tuberculosis.

In this series the spleens from forty-five cases of acute infection were examined. Of these, twenty-six showed a hyaline degeneration involving either the intima or media or both, which lesion stained poorly with the fat stain. Ten of the forty-five showed fat droplets in the muscle fibers of the media. The hyaline change occurred in 100 per cent. of the cases of tuberculosis, pneumonia, diphtheria and glanders with the exclusion of subjects under 1½ years.

In the septicemia group only 58 per cent. showed this change. The fat droplets of the media fibers were more unevenly distributed (as regards the disease) than in the renal arteries, and therefore are even less characteristic of acute infections than in the renal arteries. On the other hand, the hyaline change seems quite characteristic of cer-

tain acute infections, and must have some relation to the toxins of the disease, because in some long illnesses in which metabolic disturbances might be expected it does not occur.

The aortas were examined in thirty-six cases, twenty-one of which showed thickening of the intima with fat in nineteen of them. The fat was usually more marked in the thickened areas. Eleven of them showed fat droplets in the media muscle fibers. In 100 per cent. of the cases of tuberculosis, typhoid, pneumonia and glanders, with the exception of subjects under 1½ years, the intimal lesion was present. It was present also in most of the diphtheria and septic cases. Here again, as there were cases of other acute illnesses in which the lesion did not occur, it seems probable that there is some relation between the acute infection and the lesion.

The next point to consider is what will be the final result of these lesions. Will the lesion on healing leave the arterial system permanently impaired?

The lesion of the fat droplets in the muscle fibers of the media should clear up without permanent injury except in those fibers in which actual necrosis has occurred. If necrosis has occurred there is probably some injury also to the fibroblasts, and connective tissue replacement of the necrotic muscle will occcur.

The hyaline degeneration in the intima and media of the splenic arteries probably will not return to normal without leaving some sclerosis. In the intima of the aorta, fat without thickening may return to normal without leaving permanent evidence of a former lesion, but when the intima is thickened, either from edema, infiltration with endothelial cells containing fat, or connective tissue overgrowths, it probably will not resume its former condition, but will always show more or less sclerosis. Therefore, these lesions, which from their frequency probably bear some relation to acute infectious diseases, may leave a permanent change in the arterial system.

If, as some assert, the arteriosclerosis of old age is due to pressure relations, it is perfectly possible for these above described lesions to impair the elasticity of the vessel walls and change the size of the lumen of the vessels and thus effect the pressure relations. The sclerosed patches resulting from these lesions may impair the nourishment to the arterial wall so that a gradually progressing degeneration of the arterial system goes on which may be the cause of arteriosclerosis of old age. The sclerosis of old age may simply be a summation of lesions of this nature arising from infections or metabolic toxins in which case these lesions would play their share in the formation of the arteriosclerosis of old age.

On the other hand, these lesions, after becoming sclerosed, may have no further effect on the arterial system. The arteriosclerosis of old age

may be a disease which has an etiology entirely independent of any of the above-mentioned factors.

At the time when this study of human material was being carried on, an attempt was made to produce lesions in animals by the use of toxins. As so much discussion has been raised over the use of rabbits for experimental arterial lesions, guinea-pigs were used in this work. Some experimenters have used this animal and report positive results.

Guinea-pigs under 3 months of age were injected with vaccines of typhoid bacilli and staphylococci. These vaccines were not especially virulent, and could be given in large doses without causing the death of the guinea-pig. Three pigs were injected on five successive days with doses varying from 2,500 to 5,000 million dead staphylococci, and three others on the same days with from 2,500 to 7,000 million dead typhoid bacilli. On the sixth day these animals were killed instantaneously without anesthesia, together with three control animals. Tissue from the aorta, kidney and spleen was preserved, cut and stained just as the human material. No lesions were found in the vessels of either set of animals nor in the controls, except in the aorta of one guinea-pig injected with staphylococci, in which a thickening of the intima with connective tissue at one place occurred. Three guinea-pigs were also injected with the same amount of staphylococcus vaccine, and three others with the same amount of typhoid vaccine twice a week over a period of two months in order to see if a more prolonged action would have any effect. Both these sets of pigs were smaller and thinner than the controls kept under the same conditions, which suggested that these animals were influenced by the action of the toxins. These pigs and the controls were killed, and their tissues preserved and studied in the same manner as the others, but no lesions were discovered in the arteries.

Some experiments were done with white rats by injecting living cultures of diphtheria and typhoid bacilli and staphylococci, and also by injections of 95 per cent. alcohol. A few of the rats were quite old and the others young. As no arterial lesions appeared in any of the animals, the details of the experiments will not be recorded here.

It seems fair to conclude that in certain of the acute infectious diseases, diffuse arterial lesions exist which may be the result of toxic action. In other acute infections no arterial lesions occur. Some of these lesions will undoubtedly leave on healing a permanent sclerosis in the arterial system.

Toxins will cause arterial lesions locally at the site of the active process of the infectious disease (other authors) or locally in some distant organ such as the kidney, as was seen in the above case of scarlet fever.

Of the acute infections, diphtheria, pneumonia, tuberculosis, typhoid and glanders seemed most consistently to have associated with them general lesions in the arteries of at least one of the tissues examined.

Attempts to produce widely distributed arterial lesions in guinea-pigs and rats by means of certain bacterial toxins failed.

For the material and many kind suggestions I am indebted to Dr. F. B. Mallory.

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THE DIAGNOSTIC IMPORTANCE OF ALBUMIN AND ALBUMOSE IN THE SPUTUM AND THEIR RELATION TO OCCULT BLOOD*

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Researches in the chemistry of the sputum have not kept pace with those made in the study of the excretions and secretions of other organs of the body, and what has been done has not been found of much value to clinicians, partly because of elaborate technic and partly because of uncertainty in results obtained.

For a critical review of the work published along this line the reader is referred to an article by Wanner,[1] in which he reports a comprehensive study of the sputum from various pulmonary conditions, such as chronic bronchitis, bronchiectasis, pulmonary tuberculosis, pulmonary infarct, gangrene and pneumonia, devoting special attention to the albumin and albumose content.

He regards any albumin reaction which is more than a slight opalescence as pathological, and if there is any albumin with the heat and acid test, then the sputum ceases to be a secretion. In other words, the underlying morbid process is not bronchitis. In distinguishing between this condition and pulmonary tuberculosis, the presence of albumin speaks unconditionally in favor of tuberculosis.

As to the origin of albumin, Wanner calls attention to three sources from which it may be derived, namely, from the glands of the mucous membrane, from the blood-vessels of the bronchial tree, and from ulceration of the bronchi or the lung parenchyma. Albumose he regards as a split product of albumin, produced by bacteria and autolysis.

Recently Roger and Levy-Valensi[2] have called attention to the value of examining sputa for albumin and they claim to have discovered in the qualitative detection of protein a uniformly reliable means of diagnosing tuberculosis from bronchitis, pulmonary emphysema and conditions as syphilis, gangrene and cancer. Their studies have been

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*From the laboratory of Dr. John H. Musser.

*Read before the Pathological Society of Philadelphia March 23, 1911.

1. Wanner: Beiträge zur Chemie des Sputums, Deutsch. Arch. f. klin. Med., 1903, lxxv, 347.

2. Roger and Levy-Valensi: Albumino réaction des expectorations, Presse med., 1910, p. 289.

corroborated by Wourmann, Oddo and Gachet, and by Cornu (all quoted by Roger)[2] and most recently by Geeraerd.[3]

The last-named author is particularly enthusiastic about the test and goes so far as to say that if a case of tuberculosis presents no albumin in the sputum, it is proof of cicatricial contraction, and should albumin appear a new cure should be begun. He lays especial emphasis on coupling the chemical examination of the sputum with the cutaneous reaction, and should albumin and the latter be present, then tuberculosis is present beyond peradventure of a doubt.

The papers of Roger and Levy, and others, were so optimistic about the reliability of the albumin test, and the field of sputum chemistry has been so wofully neglected, that I have been induced to take up studies along similar lines.

Sputa containing macroscopic blood were, of course, discarded, and for our first thirty-five cases this was the only precaution observed. To our surprise practically every sputum contained either albumin or albumose, or both, and my attention was directed to the possible contamination of the sputum by small quantities of blood, which might be invisible macroscopically or microscopically, but which we might recognize by means of a subtle chemical test.

TECHNIC

A portion of sputum was collected in a large dry bottle, mixed with equal parts of water, and thoroughly stirred with a glass rod. The sputum should not be allowed to stand in a warm place, since putrefactive changes readily occur and albumin is split off from the mucus.[2] A few drops of acetic acid are now added to precipitate the mucus, and this part of the procedure must be performed with extreme care. To make sure of this, a small portion should be filtered and to the filtrate one or two drops of acetic acid added. If no cloud appears, the precipitation has been complete. Too much acetic acid may prevent the coagulation of albumin.

The sputum is now filtered and, to one portion, saturated salt solution is added, the solution boiled and one or two drops of acetic acid added. In the presence of albumin a cloud appears. To a second portion is added one drop of a saturated solution of potassium ferrocyanid which will precipitate the albumin.

Albumose.—A portion of the filtered sputum is mixed with an equal portion of a saturated solution of sodium chlorid, boiled and filtered.

3. Geeraerd: L'albumino réaction de l'expectoration chez les tuberculeux, Jour. med. Bruxelles, 1910, 505.

One portion is kept hot and the other cooled, and if albumose is present, there appears a cloud in the cooled portion.

Occult Blood.—Application of the benzidin test was made (Goodman[4]). A portion of the sputum after mixing with equal parts of water is thoroughly shaken with glacial acetic acid. The solution is then boiled, cooled and tested with benzidin. Occult blood was adjudged present when there was a distinct blue color imparted to the particles of sputum or to the liquid as a whole.

The tuberculous cases have been arbitrarily divided into incipient and advanced. Under the first heading are grouped those cases of infiltration with but few physical signs, while under the second heading are arranged those cases presenting consolidation of one or more lobes, with or without cavity formation.

The first thirty-five cases, in view of the later findings, have been rejected, and in the cases on which our study is based, the following examinations have been made: Albumin, albumose, microscopic for erythrocytes, occult blood and tubercle bacilli. The cases we have arranged in five tables, a study of which will prove of more than passing interest.

In the first place it will be seen that in the vast proportion of cases, occult bleeding, albumin and albumose go *pari passu,* and it must be recognized that minute extravasations of blood constitute the chief source of the albumin content of the sputum.

In the second place, microscopic examination of the expectoration in itself does not constitute sufficient data on which to decide whether the sputum does or does not contain blood. A final opinion can be reached only after chemical tests have been made.

Thirdly, neither albumin nor albumose is in itself significant of pulmonary tuberculosis, since we have found both present in other conditions (bronchitis, asthma, emphysema, pleurisy, heart disease). Its absence is likewise not indicative of the non-tuberculous nature of the condition, since in many cases of tuberculosis, no albumin has been found.

An interesting point is that occult bleeding is seen in many cases of incipient tuberculosis and is not a feature alone of the advanced stages. It seems to bear no relation to the presence or absence of tubercle bacilli.

In fifteen of our cases, either albumin or albumose, or both, were present when no occult blood could be detected, and we have no explanation for this phenomenon. Likewise we are at a loss to interpret the four

4. Goodman: The Examination of the Feces for Occult Blood, with Special Reference to the Value of the Benzidin Test, Am. Jour. Med. Sc., 1907.

cases whose sputa contained blood, but did not respond to the qualitative tests for albumin or albumose.

In conclusion the following statements may be made:

1. To albumin must not be ascribed such great diagnostic importance as has been ascribed by Roger and his followers.

2. It may or may not be present in the sputum of pulmonary tuberculosis.

3. It is frequently seen in benign affections.

4. In the majority of cases, minute extravasations of blood are the source of the protein. These may be so insignificant as to be invisible to the eye, and can be recognized only by chemical tests.

TABLE I.—INCIPIENT TUBERCULOSIS

No.	Albumin	Albumose	R. B. C.	Occult Blood	T. B.	
1	0	0	0	Very slight trace	0	
2	+	0	0	Present	0	
3	+	+	0	0	+	
4	+	+	0	Slight trace	0	
5	0	0	0	0	0	
6	+	+	Few	Trace	0	
7	+	+	0	Slight trace	0	
8	+	+	0	Slight trace	0	
9	+	+	0	Slight trace	0	
10	+	+	0	Slight trace	0	
11	0	0	0	0	0	
12	0	0	0	0	0	
13	0	0	0	0	0	
14	+	+	0	Slight trace	+	
15	0	0	0	0	0	
16	+	+	0	0	0	
17	Slight tr.	Slight tr.	0	0	0	
18	+	+	0	0	+	
19	+	+	0	0	+	
20	+	0	0	0	0	
21	0	0	0	0	0	
22	+	Slight tr.	Few	Trace	+	
23	0	0	0	0	0	
24	0	0	0	0	0	
25	+	+	0	Strong	+	
26	+	+	0	Strong	+	
27	+	+	0	Trace	0	
28	0	0	0	0	+	
29	+	+	0	0	0	
30	Much	+	+	Strong	+	
31	+	Trace	0	Trace	+	
32	+	+	?	Strong	0	
33	0	0	0	0	+	
34	+	+	0	0	?	
35	0	0	0	0	0	
36	+	+	0	Strong	+	
37	+	+	0	0	0	Healed

TABLE 2.—ADVANCED TUBERCULOSIS

No.	Albumin	Albumose	T. B. C.	Occult Blood	T. B.
1	+	+	?	+	+
2	+	+	0	+	+
3	+	+	0	+	+
4	+	+	0	+	+
5	+	+	Few	+	+
6	+	+	0	0	+
7	+	+	Few	+	+
8	+	+	0	+	+
9	+	+	+	Strong	+
10	+	+	0	+	+
11	+	+	+	+	+
12	+	+	Few	+	+
13	+	+	Many	+	+
14	+	+	0	+	+
15	+	+	Few	Strong	+
16	+	+	0	Strong	+
17	+	+	0	Strong	+
18	+	+	0	Strong	+
19	+	+	0	Trace	+
20	+	+	Many	Strong	+
21	+	+	Many	Strong	+
22	+	+	+	+	+
23	+	+	0	+	+
24	+	+	0	Strong	0
25	+	+	0	+	0
26	+	+	0	+	+
27	+	+	0	Trace	+
28	+	+	0	Trace	0
29	+	+	0	+	+
30	+	+	0	+	+
31	+	+	0	+	+
32	+	+	0	+	+
33	+	+	Few	+	+
34	+	+	0	+	+
35	+	+	?	Trace	+
36	+	+	0	Strong	+
37	+	+	0	Trace	+
38	+	+	0	0	+

TABLE 3.—NON-TUBERCULOUS CASES

No.	Albumin	Albumose	R.B.C.	Occult Blood	T. B.	Diagnosis
1	+	+	0	+	0	Pneumonia
2	+	+	0	0	0	Pneumonia
3	+	+	0	0	0	Pneumonia
4	+	+	Few	+	0	Pneumonia
5	+	+	Few	Strong	0	Pneumonia
6	+	+	Few	Strong	0	Pneumonia
7	0	0	0	Trace	0	Pneumonia
8	+	+	0	Trace	0	Pneumonia
9	0	0	0	0	0	Pneumonia
10	+	0	0	Very slight trace	0	Pneumonia
11	0	0	0	0	..	Bronchitis
12	+	+	0	Strong	..	Bronchitis
13	0	0	0	0	..	Bronchitis
14	0	0	0	0	..	Bronchitis
15	+	+	Few	Strong	..	Bronchitis
16	0	0	0	Slight trace	..	Bronchitis
17	0	0	0	0	0	Bronchitis
18	0	0	0	0	0	Bronchial asthma
19	+	+	0	+	0	Bronchial asthma
20	+	+	0	Trace	0	Bronchial asthma
21	+	0	Few	Strong	0	Bronchial asthma

TABLE 3.—NON-TUBERCULOUS CASES (Continued)

No.	Albumin	Albumose	R.B.C.	Occult Blood	T. B.	Diagnosis
22	0	0	0	0	0	Bronchial asthma
23	0	0	0	0	0	Pleurisy
24	+	+	0	Very slight trace	0	Pleurisy
25	+	+	0	Slight trace	0	Empyema
26	+	+	0	Very slight trace	0	Gastritis
27	+	0	Few	Trace	0	Hyperchlorhydria
28	+	+	Few	Trace	0	Heart disease
29	0	+	0	0	0	Hereditary syphilis

TABLE 4.—TUBERCULOUS CASES WITH ALBUMIN AND ALBUMOSE BUT NO OCCULT BLOOD

No.	Albumin	Albumose	R.B.C.	Occult Blood	T. B.	Diagnosis
1	+	+	0	0	+	Advanced
2	+	+	0	0	+	Advanced
3	+	+	0	0	0	Incipient (healed)
4	+	+	0	0	0	Incipient (healed)
5	Slight tr.	Slight tr.	0	0	0	Incipient (healed)
6	+	+	0	0	+	Incipient (healed)
7	+	+	0	0	+	Incipient (healed)
8	+	0	0	0	0	Incipient (healed)
9	0	Trace	0	0	0	Incipient (healed)
10	+	+	0	0	0	Incipient (healed)
11	+	+	0	0	?	Incipient (healed)
12	+	+	0	0	0	Incipient (healed)

TABLE 5.—NON-TUBERCULOUS CASES WITH ALBUMIN AND ALBUMOSE BUT NO OCCULT BLOOD

No.	Albumin	Albumose	R. B. C.	Occult Blood	Diagnosis
1	+	+	0	0	Pneumonia
2	+	+	0	0	Pneumonia
3	0	+	0	0	Hereditary syphilis

TABLE 6.—CASES OF OCCULT BLOOD BUT WITH NO ALBUMIN OR ALBUMOSE

No.	Albumin	Albumose	R. B. C.	Occult Blood	T. B.	Diagnosis
1	0	0	0	Slight tr.	0	Advanced tuberculosis
2	0	0	0	Slight tr.	0	Bronchitis
3	0	0	0	Very slight tr.	0	Incipient tuberculosis
4	0	0	0	Trace	0	Pneumonia

I am indebted to Drs. Landis, Francine, Corson and T. Mellor Tyson for placing material at my disposal. Use has been freely made of sputa obtained from cases in the private practice of Dr. Musser and in his ward in the Presbyterian Hospital.

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EXPERIMENTS WITH THE INTRAVENOUS INJECTION OF SALVARSAN IN ACID SOLUTION *

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INTRODUCTION

In the vast literature already existing about Ehrlich's wonderful discovery there is little experimental evidence on the action of salvarsan in acid solution when given intravenously. The drug has been occasionally given in this form to human beings by a few clinicians, but their results need not concern us here, for it is obvious that the best method for administering an admittedly toxic substance cannot be thoroughly tested on human beings. These considerations made it desirable to investigate this aspect of the subject, and therefore the tolerance of rabbits for salvarsan was tried out when this substance was dissolved in 0.9 per cent. salt solution and injected intravenously. Practically the only experimental contribution which demands consideration here has been the work of Hering,[1] who tested the effect of 606 when dissolved in 0.9 per cent. saline so as to form a 0.5 per cent. solution.

This solution was infused through the jugular vein of rabbits and dogs, and their blood-pressure recorded. This author found that 4 to 5 mg. per kilo rabbit, infused during five to ten minutes, caused death one-half to two minutes after stoppage of the infusion. Similar results were obtained with dogs. On the basis of this experimental evidence he warns earnestly against the employment of acid solutions in human therapeutics. In the following pages experimental evidence will be brought forward to show that Hering's warning is applicable only to the acid solution in 0.5 per cent. strength; it emphatically does not apply to the acid solution of salvarsan when sufficiently dilute, for example, in a strength of 0.1 per cent.

EXPERIMENTS

Methods.—All the experiments were carried out by the intravenous infusion of the drug in rabbits. The solutions were injected either into the jugular vein or the marginal ear vein. When the injection was given into the jugular vein, the animal was first etherized, in order to insert the venous and arterial cannulas. After recovery from the anesthetic, the solution was allowed to flow into the vein from a Mariotte burette at

*From the Department of Physiology and Pharmacology of the Rockefeller Institute.

1. Hering: München. med. Wchnschr., 1910, lvii, 2621.

a pressure of about 15 cm. of water. The blood-pressure was usually recorded by a mercury manometer connected with the carotid artery, the tubing being filled with a half-saturated solution of sodium sulphate.

The solution of salvarsan was always prepared by grinding the powder in a sterile mortar with gradually increasing quantities of sterile 0.9 per cent. saline, until a clear solution of the required strength was obtained. This initially clear solution always showed a moderate opalescence after some hours. After a sealed tube of salvarsan had been opened, the substance was used as a rule within a few hours; if any remained, it was discarded. No solution was ever utilized which had been prepared the previous day.

The first two series of experiments need but little discussion; the main results will be seen in the subjoined tables. In the first series a 0.25 per cent. solution of salvarsan was infused through the jugular vein. Both animals died after receiving per kilo respectively 41 and 57 mg. One died twenty-five minutes after stoppage of the infusion, with tonic and clonic convulsions; the other died during the night.

In the second series a solution of 0.5 per cent. strength was infused slowly through the jugular vein. Four out of five animals succumbed after receiving a much smaller dose per kilo body-weight than when the solution, as in Series 1, was half as strong. Further details will be seen in Table 2.

These two series of experiments show clearly the effect of concentration of solution on the size of lethal dose: with 0.25 per cent. strength (Series 1) the animals needed from 40 to 50 mg. per kilo body-weight; with a solution twice as strong, viz., 0.5 per cent., the lethal dose varied between 4 and 16 mg. per kilo weight. In other words, if the infused solution was diluted twofold (0.5 per cent. to 0.25 per cent.) the maximal tolerance was increased over four times (10 mg. to 40 mg.). It therefore seemed possible that a still greater dilution would permit the infusion of fairly large amounts of salvarsan and yet save the animal. It may be stated at once that this expectation was realized when the infusions were carried out with 0.1 per cent. strength. Table 3 (Series 3) gives a brief summary of this experiment.

These animals, during and after the infusion of about 12 mg. per kilo, were never in any obvious danger. During the infusion the respiration was slowed, but the blood-pressure remained practically at the normal level. All of the animals were in good condition at least sixteen days after the injection. It will be seen, however, that the infusion rate was exceedingly slow, at times less than 0.5 c.c. per minute. The exceeding slowness of this rate will be realized when one considers that 0.5 gm. of salvarsan would thus require over sixteen hours for its infusion. Such a method of introducing a drug is therefore only of academic value, provided that the infusion rate cannot be increased. To test this another

series of experiments was carried out (Series 4) in which the attempt was made to inject large quantities per kilo in a shorter time than in the experiments of Series 3; in addition it was also determined whether the acid solution causes pain and irritation when injected into a superficial vein, especially if some of the solution should escape into the adjacent tissue. These injections were made with 0.1 per cent. solutions injected by means of a syringe into the marginal ear vein of non-anesthetized rabbits.

This last series shows very well that a comparatively large dose of salvarsan in acid solution may be injected intravenously with fair rapidity in rabbits without causing pain or obviously endangering the animals' lives. The muscular weakness which was noted in Series 3, in which the animals were anesthetized in order to insert cannulas into the external jugular vein and into the carotid artery, was markedly less pronounced in the animals comprising Series 4, when the injections were carried out minus anesthesia or operative interference.

DISCUSSION

In the foregoing pages experimental evidence has been submitted which shows that the toxicity of salvarsan in acid solution (viz., simply dissolved in 0.9 per cent. saline) when injected intravenously in rabbits varies inversely with the concentration of this substance in the solutions employed. Thus for example, when salvarsan was injected in 0.5 per cent. solution (Series 2), four out of five animals died on the holder after receiving 4 to 16 mg. per kilo, while in Series 3, and especially in Series 4, the rabbits tolerated 10 to 22 mg. per kilo in 0.1 per cent. solution without any marked evil effects. Moreover, all the animals of these two series (eight rabbits) were alive and well at least sixteen days after the injection. In order to emphasize the amount injected it may be permissible to express this result in terms of a 70-kilo person. Such a person would easily tolerate, on the basis of these data, 0.7 to 1.5 gm. of salvarsan when given intravenously in 0.1 per cent. acid solution. It must be emphasized that the above doses for rabbits are by no means the maximal doses of the 0.1 per cent. solution which are just tolerated with safety; although I have no experiments to support this statement, it seems probable to me that still larger amounts may be injected before seriously endangering the animal's life.

From the tables of Series 4 it will be seen that the rate of injection is still fairly slow, the fastest rate employed being 6 c.c. per minute, and the slowest about 3 c.c. per minute. This rate can be doubled without trouble or danger. In five reinjection experiments, 20 mg. of salvarsan per kilo in 0.1 per cent. solution were introduced through the ear-vein at a rate of 15 c.c. per minute; the animals showed no distress. At this rate 0.5 gm. could be incorporated in a little over half an hour.

TABLE 1.—SERIES 1: RABBITS INJECTED WITH 0.25 PER CENT. SALVARSAN IN 0.9 PER CENT. SALINE; JUGULAR VEIN

No.	Color	Sex	Weight	Blood-Pressure Before Infusion	Blood-Pressure After Infusion	Rate of Infusion c.c. per	Mg. per Kilo	Result*
..	....	..	...					.....
..	....	..	...					.....
..	....	..	...	.....	sion	c.c. per	....	.....
..	....	..	gm.	mm.	mm.	mm.	....	.....
S4	White	F	1,670	114	60	1	41.8	Very weak; next a. m. found dead.
S5	White	F	1,400	100	40	1	57	Strong convulsions after infusion. Death twenty-five minutes after infusion.

*Rate of infusion less than 1 c.c. per minute.

TABLE 2.—SERIES 2: RABBITS INJECTED WITH 0.5 PER CENT. SALVARSAN IN 0.9 PER CENT. SALINE; JUGULAR VEIN

No.	Color	Sex	Weight	Blood-Pressure Before Infusion	Blood-Pressure After Infusion	Rate of Infusion c.c. per	Mg. per Kilo	Result*
..	....	..	...					.....
..	....	..	...					.....
..	....	..	...	.....	sion	c.c. per	....	.....
..	....	..	gm.	mm.	mm.	mm.	....	.....
S3	Gray	F	3,290	90	8	1	8.	B.-P. dropped suddenly after 6.25 c.c. short convulsions. Resp. and heart stopped.
S6	White	F	1,260	84	66	0.5	16.6	B.-P. still 66 mm. Hg. Now 4 c.c. of solution ran in swiftly by accident.
S7	White	F	1,570	104	72	0.33	12.7	After a three-min. stoppage of infusion a few drops of solution caused a sudden fall of B.-P. to almost zero. Death.
S8	White	F	1,440	104	66	0.2	6.9	Infusion stopped for 18 min. B.-P. maintained at about 70 mm.; now after a few drops of sol. B.-P. dropped to 26 mm. Stop infusion. Recovery.
S9	Gray	F	2,470	110	30	0.2	4	B.-P. slowly sank to 30 mm. Convulsions, heart irregular; resp. stopped. Death.

*B.-P. means blood-pressure.

TABLE 3.—SERIES 3: RABBITS INJECTED WITH 0.1 PER CENT. SALVARSAN IN 0.9 PER CENT. SALINE; JUGULAR VEIN

No.	Color	Sex	Weight	Blood-Pressure Before Infusion	Blood-Pressure After Infusion	Rate of Infusion c.c. per	Mg. per Kilo	Result
..	....	..	...	.....	.....	....	....	.....
..	....	..	...	.....	.....	....	....	.....
..	....	..	...	.....	.....	....	....	.....
..	....	..	gm.	mm.	mm.	mm.	....	.....
S10	Gray	F	2,790	104	104	0.6	10.7	Moderately weak after infusion; moves about. Good condition 2 days later.
S11	Gray	F	1,440	100	105	0.5	11.1	Hops about after infusion; some weakness. Good condition 2 days later.
S12	Gray	F	1,760	96	90	0.5	14.2	Moderate weakness after infusion. Good condition next day.
S13	Gray	M	2,330	116	108	0.8	12.8	Moderate weakness after infusion. Next day in good condition.

TABLE 4.—SERIES 4: RABBIT INJECTED WITH 0.1 PER CENT. SALVARSAN SOL. IN 0.9 PER CENT. SALINE; MARGINAL EAR-VEIN

No.	Color	Sex	Weight	Rate of Infusion c.c. per	Duration of Infusion	Mg. per Kilo	Result
..	....	...	.....	.....	.....	.....	.....
..	....	...	.....	.....	.....	.....	.....
..	....	...	gm.	min.	min.	....	.....
S14	White	F	2,110	6	5.5	15.5	No struggle or pain during infusion. Hops about at once after injection. Respiration slowed.
S15	Gray	F	1,400	3.6	8	21.4	Perfectly quiet during injection. Resp. slowed. After the injection quiet; ears erect.
S16	Gray	F	1,350	3.3	9	22.2	Two short struggles during injection. Resp. slowed. Moves about after injection; ears erect.
S17	White	F	2,200	3	12	15.9	Slight short struggle during injection. Moves about after injection; ears erect. Practically no slowing of respiration.

Another point of interest noted in the series of animals which received the drug through the ear-vein was this: none of the animals showed any pain whatsoever during or after the injection, nor did any marked inflammation or necrosis result. This was especially striking in one animal, S17, in which some of the injected solution accidentally infiltrated a small area of tissue. No edema or marked inflammation occurred at any time during the next twelve days. The marginal ear-vein merely became thrombosed, and later showed a slight degree of inflammation, such as is usually observed after any injection into this vein. A much severer reaction at the site of injection was expected because of the technic I employed; the hypodermic needle was always inserted 1.5 to 2 cm. into the vein and then anchored by two bulldog clamps which gripped the ear and the needle. This more or less marked crushing of the tissues, especially of the injected vein itself, would surely aid in bringing out whatever irritating qualities the injected solution possessed. In spite of this none of the rabbits showed pain at any time, and in no rabbit did any marked inflammation occur, even when some of the 0.1 per cent. solution infiltrated the wall of the vein and the surrounding tissue. In but one rabbit (S16) did moderate edema of the ear occur. This edema was noted within twenty-four hours after the injection and was by no means extreme; twenty-four hours later it had disappeared entirely.

It may be remarked in passing that the acid content of salvarsan is very small, only 83 mg. of hydrochloric acid per 0.5 gm. This amount in a 0.1 per cent. solution of the drug makes an exceedingly dilute solution of the acid, so dilute that the alkaline tissue juices can have no trouble in reducing and neutralizing the acidity of the solution which escapes into the surrounding tissue. This is an advantage not possessed by the strongly alkaline solutions generally employed.

OTHER OBSERVATIONS

While the main object of this investigation was to determine the conditions under which fairly large quantities of an acid solution of salvarsan could be safely infused in rabbits, a number of other data were gathered during the course of the work which are worthy of being recorded.

Autopsy Notes.—In practically all the fatal cases in Series 1 and 2 there was an excess of clear yellow fluid in the peritoneal cavity and in the thorax. This was especially well marked in the two rabbits of Series 1. No excess of fluid was seen in the intestine itself. The intestines were, as a rule, pale, while the mesenteric vessels were moderately distended with blood. The lungs in almost all instances showed signs of pulmonary edema, which, however, was never so extreme that foam was found in the trachea. The heart usually was distended with blood when the autopsy was made immediately and was in a state of block, the auricles beating three or four times to one weak ventricular contraction. The blood coagulated readily within three to five minutes.

Urine.—Most of the surviving animals voided urine within the twenty-four hours following the injection. In one rabbit only (S8) about forty-eight hours elapsed before urine was passed; this rabbit was the only one which survived when the drug was given in 0.5 per cent. solution; all the other survivors belonged

to the 0.1 per cent. series. None of the urines voided by these surviving rabbits reduced copper solution. Only one rabbit showed sugar in the urine; this was Rabbit S4, which received over 41 mg. of salvarsan per kilo in 0.25 per cent. solution. This rabbit died during the night, and the urine obtained from its bladder showed 2.5 per cent. sugar according to Pavy's method. It will be remembered that this rabbit also showed a large excess of free fluid in the peritoneal and pleural cavities.

Weight.—All of the surviving rabbits were carefully weighed at regular intervals after the injection. It soon became apparent that the members of the two series, 3 and 4, reacted differently, although both received the drug in the same concentration. The rabbits of Series 3 all showed, during the first few days, an initial loss of weight which varied between 130 and 230 gm., and normal weight was not regained until about ten days had passed. The rabbits of Series 4, on the other hand, showed in three cases (S14, S15, S16) a gain of weight in three days varying between 160 and 470 gm.; this initial increase was well maintained, so that twelve days after the injection their weights were still 150 to 300 gm. above normal. The fourth rabbit of this series showed a loss of 90 gm. one day after injection, but this loss was repaired within five days. It must be added that no surviving rabbit of any series showed diarrhea at any time.

This difference in reaction to the same solution, for both series received the drug in 0.1 per cent. strength, is probably due to the different methods employed. In Series 3 the animals were subjected not only to the depressing effect of salvarsan but also to the unfavorable action of the ether, operation, etc.; while animals of Series 4 were exposed to the effects of salvarsan alone. This result is interesting, for it indicates that even normal animals when injected with the same solution under different conditions may show fairly striking differences in the end-result.

Fall of Blood-Pressure.—Another point of interest, which was brought out by the blood-pressure experiment of Series 2, is this: with fairly concentrated solutions, 0.5 per cent. in this instance, the blood-pressure may sink profoundly without any warning. In the experiments S3, S7, S8, the blood-pressure suddenly dropped markedly. In two animals this ended with death; one recovered. The blood-pressure before this drop was still good, ranging between 65 and 80 mm. of mercury, and there was nothing to indicate a weakening of the heart. Moreover the fall occurred in two cases on resuming the infusion which had been stopped for a number of minutes. This drop of blood-pressure is probably due to a sudden weakening of the heart. These three experiments show well how swiftly a dangerous and even fatal fall of blood-pressure may occur with 0.5 per cent. solutions, even when infused with extreme slowness.

Reinjection Experiments.—A number of the surviving rabbits were again injected with the 0.1 per cent. acid solution. Thus S8, S11, S14, S15, S16 received 20 mg. of salvarsan per kilo body-weight, sixteen to twenty days after the first injection. The reinjection was given through the marginal ear-vein at a rate varying from 10 to 17 c.c. per minute. The animals were quiet after the injection, and the respiration was considerably slowed, ranging between 50 and 80 per minute. The temperature always showed a rise of at least 1° C. within two or three hours after the injection; the highest temperature obtained was 41.5 C. The average normal temperature was about 39.5 C. This period of fever did not last long as a rule; after less than twenty-four hours the temperature had dropped to normal. It deserves notice that the slow respiratory rate mentioned above was also obtained during the stage of fever. All the rabbits stood the heavy dose of salvarsan very well, and no ill effects were seen except that S16 developed a massive edema of the injected ear; this edema disappeared within three days. In none of the other rabbits did an edema appear. It will be remembered that the same rabbit, S16, reacted with a moderate edema to the first injection of salvarsan.

RESULTS

Acid solutions of salvarsan, i. e., salvarsan dissolved in 0.9 per cent. saline solution, may be injected intravenously in rabbits with safety provided that the solution is dilute.

With a 0.1 per cent. solution in 0.9 per cent. saline as much as 22 mg. and probably more per kilo may be safely infused; this would correspond in a 70 kilo individual to 1.5 gm.

Concentrated solutions of salvarsan in saline, i. e., 0.5 per cent., are dangerous and usually fatal in rabbits even when infused with great care; the fatal dose varies between 4 and 12 mg. per kilo. This agrees practically with the experimental results obtained by Hering.

The acid solution in 0.1 per cent. strength causes no pain or marked inflammation when injected into the ear-vein of rabbits, even when some of the solution infiltrates the surrounding tissue.

Hering's energetic warning against the intravenous injection of acid solution of salvarsan in human beings has experimental justification only for 0.5 per cent. solutions of the drug. It does not apply to sufficiently dilute solutions, for example, solutions of 0.1 per cent.

Attention may be called to the fact that 0.5 gm. of salvarsan contains only 0.083 gm. of hydrochloric acid, a quantity which corresponds to about 0.25 c.c. of the ordinary 32 per cent. concentrated acid. A 0.1 per cent. solution of the drug is therefore only weakly acid. It also must be noted that the tissues of the body are better able to protect themselves against harmful acidity than against harmful alkalinity; against an acid solution the body tissues may mobilize neutralization and dilution; against harmful alkalinity practically only dilution is available, the carbon-dioxid content of most tissues being probably too small to play much of a rôle.

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URINE FORMATION DURING ETHER ANESTHESIA*

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In a previous paper[1] I reported the data from a series of experiments on the diuresis following ether anesthesia. In those experiments, which were made on dogs, it was shown that ether narcosis induced for periods varying in length from thirty minutes to four and one-half hours was followed in every instance by an initial diuresis, the extent of the diuresis being proportional, in some instances, to the length of the anesthesia period. This point was well illustrated by the initial diureses of 5.7 per cent., 6.8 per cent., 12.9 per cent. and 24.8 per cent. which followed ether anesthesia periods of one-half, one, two and four and one-half hours respectively. It was further shown in these experiments that the diuretic effect of the ether was persistent in every case except one. The ultimate average daily percentage increase in the urine volume ranged from 3.1 per cent. to 20.7 per cent. for subsequent intervals of from five to fourteen days.

The data from the experiments mentioned above gave us no information as to the actual conditions of urine formation during the time the animal was under the influence of the anesthetic. It was therefore subsequently determined to investigate the rate of urine formation under ether anesthesia, using in these tests the identical animals utilized in the experiments already mentioned. Three of these animals (Dogs 1, 3 and 5) were therefore made the subjects of the demonstration.

The plan of the experiments here reported was simple. The animal was placed under ether anesthesia, after which the abdomen was opened and cannulas inserted in the ureters. The rate of urine formation was then carefully observed, the volume formed during each hour being accurately measured.

DISCUSSION OF DATA

The data from the first experiment (Experiment 12) are given in Table 1. The subject of this experiment was Dog 1, a bitch weighing about 5.5 kg. Anesthesia was induced for a period of ten hours and twenty minutes during which time a urine flow aggregating 19.7 c.c. was registered. During the first two hours a volume of 1.9 c.c. was collected,

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1. Hawk: Jour. Med. Research, 1908, new series, xiii, 203.

indicating a total urine formation of 3.6 c.c. for this period, inasmuch as the two cannulas had a capacity of 1.7 c.c. The most rapid formation of urine was noted between the fourth and fifth hours of anesthesia. During this interval 5.7 c.c. of urine was formed. Following this hour there was a pronounced decrease in the rapidity of urine formation, as is shown by the subsequent collection of fractions of 4.1 c.c. and 2.4 c.c. respectively during the two one-hour periods immediately following. During the next four hours the urine-forming function was practically suspended, as is shown by the formation of only 0.5 c.c. of urine. The specific gravity of the various fractions of urine ranged from 1.028 to 1.057. This high specific gravity was due in part to the presence of dextrose, inasmuch as glycosuria accompanied the anesthesia. Analysis of a composite sample of urine showed the presence of 5.29 per cent. of dextrose. Our other data on the glycosuria following ether anesthesia have been presented elsewhere.[2]

TABLE 1.—RATE OF URINE FORMATION UNDER ETHER ANESTHESIA (DOG 1, EXPERIMENT 12)*

Fraction No.	Collected: Hour	Collected: Length of Time after Induction of Anesthesia		Volume: Fraction	Volume: Total	Specific Gravity of Fraction
	p. m.	hrs.	min.	c.c.	c.c.	
1	12:40	2	10	1.9	1.9	1030
2	1:30	3	..	2.1	4.0	1042
3	2:20	3	50	1.3	5.3	1030
4	3:10	4	40	5.7	11.0	1036
5	4:00	5	30	4.1	15.1	1028
6	4:50	6	20	2.4	17.5	1057
7	8:50	10	20	0.5	18.0	1040
8	Urine in cannulas at end of experiment			1.7	19.7	1030

*Cannulas in ureters and ether narcosis induced for ten hours and twenty minutes.

The second of our urine-formation studies (Experiment 13) was made on Dog 3, an animal weighing about 8.5 kg. The data are given in Table 2. The period of anesthesia was eleven hours and fourteen minutes in length. In this experiment 5.1 c.c. of urine were collected during the operation. The first fraction collected from the ureters was one of 1.9 c.c., which was completed in an hour and three quarters after the induction of anesthesia. The data in this regard from Experiments 12 and 13 are very similar, in that the same volume of urine was formed during very similar periods of time. The maximum urine formation occurred between the second and third hours of anesthesia in this experiment, as against a fourth-fifth hour maximum in the case of Dog 1.

2. Hawk: Postanesthetic Glycosuria, THE ARCHIVES INT. MED., 1911, viii, 39.

From the point of maximum formation a somewhat regular decrease was observed in the hourly urine formation, indicating a gradual inhibition of this function. The final fractions collected between the ninth and eleventh hours of anesthesia were 0.3 c.c. and 0.2 c.c. in volume respectively. No urine was formed during the last half hour of the test. The total volume of urine formed by this animal in a period of eleven hours and fourteen minutes was 20.7 c.c. as against 19.7 c.c. formed in the previous experiment in an interval of ten hours and twenty minutes. The specific gravity of the urine fractions varied from 1.020 to 1.054. Glycosuria was also demonstrated in this experiment, a composite sample on analysis showing 6.32 per cent. of dextrose.

TABLE 2.—RATE OF URINE FORMATION UNDER ETHER ANESTHESIA (DOG 3, EXPERIMENT 13)*

Fraction No.	Collected: Hour	Collected: Length of Time after Induction of Anesthesia (hrs.)	Collected: Length of Time after Induction of Anesthesia (min.)	Volume: Fraction (c.c.)	Volume: Total (c.c.)	Specific Gravity of Fraction
1	10:30 a. m.	..	14†	5.1	....	1020
2	12:00 m.	1	44	1.9	7.0	1022
3	12:30 p. m.	2	14	2.2	9.2	1025
4	1:00 p. m.	2	44	2.4	11.6	1025
5	2:00 p. m.	3	44	1.9	13.5	1044
6	3:00 p. m.	4	44	1.3	14.8	1046
7	4:00 p. m.	5	44	1.0	15.8	1050
8	5:00 p. m.	6	44	1.2	17.0	1054
9	6:00 p. m.	7	44	0.5	17.5	1044
10	7:00 p. m.	8	44	1.0	18.5	1038
11	8:00 p. m.	9	44	0.3	18.8	1030
12	9:00 p. m.	10	44	0.2	19.0	1034
13	9:30 p. m.	11	14	1.7‡	20.7	1030

*Cannulas in ureters and ether narcosis induced for eleven hours and fourteen minutes.
†Collected during operation.
‡Removed from cannulas at end of experiment.

The third experiment of this series (Experiment 14) was made on a bitch weighing about 6.5 kg. The time of anesthesia was twelve hours and twenty-four minutes. This experiment was marked by an almost complete suppression of urine formation throughout the period of anesthesia. Only 3 c.c. of urine were formed in over twelve hours' time. The first fraction (0.9 c.c.) was collected about four hours after anesthesia had been induced, thus indicating the actual formation of 2.6 c.c. of urine during this interval when the capacity of the cannulas is taken into account. During the following hour 0.4 c.c. of urine was formed, but from that hour until the end of the experiment, i. e., for a period of over eight hours, no urine was formed. The urine of this experiment was very concentrated as shown by specific gravities ranging from 1.050 to 1.068.

The rectal temperature of this animal (Dog 5) was taken after eleven hours under ether and found to be 23° C. or 15° below normal. This observation is right in line with similar findings by Simpson[3] in experiments on monkeys. In Simpson's experiments, however, the animal was placed in a cold chamber having a temperature of 8.8 C., whereas in our tests the animal was at room temperature. In one instance a reduction of body temperature to 14 C. was observed by Simpson, this lowering of body temperature being followed by complete recovery, whereas in another instance a reduction to 12.5 C. caused the death of the animal. The paralysis of the heat-regulating mechanism, under the influence of ether, as shown in these experiments on dogs and monkeys, is of considerable interest.

TABLE 3.—RATE OF URINE FORMATION UNDER ETHER ANESTHESIA (DOG 5, EXPERIMENT 14)*

Fraction No.	Collected: Hour	Collected: Length of Time after Induction of Anesthesia		Volume: Fraction	Volume: Total	Specific Gravity of Fraction
...	.....	hrs.	min.	c.c.	c.c.	.....
1	1:10	3	4	0.9†	....	1050
2	2:15	4	9	0.4	1.3	1055
3	10:30	12	24	1.7‡	3.0	1068

*Cannulas in ureters and ether narcosis induced for twelve hours and twenty-four minutes.
†This urine was collected entirely from the right kidney.
‡Removed from cannulas at end of experiment.

When we compare the data from the three experiments on urine formation, we find that two of them present very similar conditions. In Experiment 12, as well as in Experiment 13, the urine-formation was most rapid during the first portion of the anesthesia period. For example, in Experiment 12, in which the period of narcosis was ten hours and twenty minutes, the maximum urine flow occurred between the fourth and fifth hours, whereas in Experiment 13, in which the period of anesthesia was eleven hours and fourteen minutes, the maximum output was secured between the second and third hours. These two experiments are similar also in that the point of maximum urine formation was followed by a gradual inhibition of the urine-forming function which finally resulted in the practical cessation of all flow. The two experiments under comparison are closely comparable from the standpoint of the volume of urine formed during the anesthesia periods. The data indicate that in the first experiment 19.7 c.c. of urine were formed in ten hours and twenty minutes, whereas in the second experiment 20.7 c.c. of urine were formed in eleven hours and fourteen minutes. In other words, in one instance an

3. Simpson: Jour. Physiol., 1902, xxviii, Proceedings p. 37.

average of 1 c.c. of urine was formed every 32.5 minutes, whereas in the other instance a similar volume of urine was formed in 31.9 minutes.

When we consider the data from Experiment 14, it is at once apparent that there are few points of similarity between this experiment and the two experiments just discussed. The main point of similarity is found in the fact that the most rapid urine formation took place during the early hours of anesthesia. It will also be observed, however, that the total volume of urine formed during the experiment (3 c.c.) was only 15 per cent. as great as that formed in Experiment 12 and only 14 per cent. as great as that formed in Experiment 13. This is particularly surprising when it is remembered that the length of the anesthesia period was twelve hours and twenty-four minutes, an interval about two hours longer than the anesthesia period of Experiment 12 and about one hour longer than that of Experiment 13. It took twice as long (ten minutes) to get the subject of Experiment 13 completely under the influence of the anesthetic as it did the subjects of the other tests.

Similar inhibitions of the urine-forming function to that observed by us have been reported by Kemp[4] in experiments on dogs and by Tait[5] in connection with certain surgical procedure in which ether was the anesthetic. Seelig[6] and Goll[7] have also observed the partial suppression of urine formation under the influence of ether anesthesia. Some experiments made by Professor Gies and myself during the investigation of external hemorrhage are also of interest in this connection.[8] In one experiment the animal (dog) was placed under ether anesthesia and cannulas inserted in the ureters and the left femoral artery. The normal course of the urine formation was then observed for one hour. The animal was then subjected to a hemorrhage in which blood equivalent to 3.14 per cent. of the body weight of the animal was removed. The formation of urine gradually decreased as the blood was being withdrawn and one minute after the end of the hemorrhage the urine flow entirely ceased. In twenty minutes the flow began again. A second hemorrhage induced about three hours later was accompanied by the same features regarding urine flow. In other experiments the blood removed from the animal was defibrinated and returned. The return of this defibrinated blood was found to cause an immediate increase in the rate of urine formation, in some instances the rapidity of urine flow being greater than normal.

SUMMARY

Three experiments were made to study the rate of urine formation under ether anesthesia. Dogs were used as subjects, cannulas being

4. Kemp: New York Med. Jour., 1899, lxx, 732.
5. Tait: Brit. Med. Jour., 1880, ii, 845.
6. Seelig: Arch. f. exper. Path. u. Pharmakol., 1904-05, lii, 481.
7. Goll: Ztschr. f. rat. Med., 1854, iv, 78.
8. Hawk and Gies: Am. Jour. Physiol., 1904, xi, 228.

inserted in the ureters and the volume of urine formed for periods of from ten hours and twenty minutes to twelve hours and twenty-four minutes observed.

Two of the experiments yielded very similar data. In each instance the first portion of the period of narcosis witnessed the most rapid formation of urine, the maximum output occurring in one case between the second and third hours and in the other case between the fourth and fifth hours, the flow gradually decreasing in each instance from this point to the end of the experiment. The average excretion for each experiment was approximately 2 c.c. per hour.

The third experiment, although embracing the longest anesthesia period, was also marked by the smallest urine flow. Only 3 c.c. of urine were formed during twelve hours and twenty-four minutes of anesthesia, the flow being entirely suppressed during the last eight hours of this interval. Glycosuria was observed in each experiment.

A body temperature (rectal) of 23 C. was observed in a dog after the animal had been subjected to the influence of ether anesthesia for a period of ten hours.

Taking the data from these experiments into consideration with the data from others already reported[1] it is apparent that ether anesthesia causes an inhibition of the urine-forming function during the time anesthesia is induced, but that such inhibition is quickly followed by a stimulated urine flow which is initiated as soon as the period of anesthesia terminates.

The inhibition of the urine-forming function was probably due to the effect of the ether in constricting the arterioles of the kidney's blood-supply. A contributing factor may have been the increased affinity of the tissue colloids for water brought about through the influence of the ether, thus leaving less water to be excreted through the kidneys.[9]

9. See Fischer's Edema,, 1910, p. 194.

THE LABORATORY DIAGNOSIS OF GENERAL PARESIS

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During the past year an investigation has been made in the laboratory of the Binghamton State Hospital for the Insane, of the cerebrospinal fluid from fifty-seven patients with general paresis, for the purpose of determining the relative value of the various laboratory methods of diagnosis which are now in quite general use. The results are shown in Table 1. As a control the same tests were applied to the spinal fluid from twenty-nine patients unquestionably suffering from psychoses other than general paresis. The fluids were obtained by lumbar puncture, about 10 c.c. being removed as a rule. The patients were kept in bed for twenty-four hours after the operation and no dangerous results occurred. Headache, dizziness, backache, and sometimes nausea followed, but no more severe symptoms were noted. The spinal fluid in general paresis is clear in appearance in the great majority of cases and when not, the cloudiness is nearly always due to blood caused by the needle, and not present in the fluid, as shown by subsequent autopsy, although cloudy fluid may be found when the autopsy is not performed soon after death. Rarely is it cloudy during life in cases which are characterized by an unusual increase in the number of cells.

The reaction of the fluid is very faintly alkaline, as shown by litmus paper, and is practically constant in normal as well as pathological fluids. The slight variations in disease are not of diagnostic value, and no effort was made to determine the exact degree of alkalinity which is usually stated as corresponding to 0.1 per cent. of sodium hydrate.

Methods of estimating the pressure of the cerebrospinal fluid are unreliable and have not proved satisfactory. It is sometimes estimated by the number of drops per minute. Obviously this depends largely on the lumen of the needle used. The estimation of pressure by a water or mercury manometer is difficult and unnecessary. The various factors which influence pressure are so numerous as to render it of no value in diagnosis. The variations as stated in the tables shown here merely signify that the rate and force of flow from the needle was apparently greater or less than that observed in the average case not suffering from general paresis. The pressure shows no appreciable difference in many instances after death, the fluid flowing as freely as during life when the body is placed in the same position. In the fifty-seven cases of general

paresis examined the pressure seemed to be increased in twenty-seven cases, decreased in fifteen, and in fifteen it showed no apparent difference from that found in other forms of insanity.

Serum-albumin is usually considered as being absent in normal spinal fluid although it shows a slight cloud on heating and gives a decided ring with the nitric acid and nitro-magnesium contact tests in all cases. The latter method, in which the fluid is brought into contact in a pipette with a mixture of 25 parts of nitric acid and 75 parts of saturated solution of magnesium sulphate, is much the more delicate. These reactions are merely due to proteins and are not to be looked on as an indication of the presence of albumin. The quantitative estimation of the protein content is unsatisfactory. The Esbach albuminometer is the instrument commonly used. The amount of fluid necessary for the determination can be diminished by diluting with distilled water and allowing for the dilution in computing the result. Reference to Table 2 will show that twenty-two out of twenty-nine cases (not cases of general paresis) or 75 per cent. of the total number show from 0.03 to 0.06 per cent. of protein by the Esbach method. The amount of protein in normal spinal fluid is given by Mott as 0.03 per cent. In the cases of general paresis Table 1 will show that forty-four of the fifty-seven cases, or 77 per cent., gave over 0.06 per cent., and twenty-nine over 0.1 per cent. of protein by the Esbach albuminometer. This would seem to be an important although a slow method of diagnosis unless the centrifuge is used.

It will be observed that sugar was found in practically all cases without any reference to the form of insanity. It is now conceded by Halliburton to be present in normal fluid and is said to occur in smaller quantities in dementia præcox. The amount of fluid necessary for a quantitative examination renders it impracticable for diagnostic purposes. In the last annual report of the Binghamton (New York) State Hospital,[1] attention was called to the interesting fact that sugar is usually absent in post-mortem spinal fluid.

In all cases of general paresis a considerable excess of globulin is found in the cerebrospinal fluid. This is usually readily demonstrated by the butyric acid test of Noguchi. Two parts of spinal fluid are heated to the boiling point with five parts of a 10 per cent. solution of butyric acid in either distilled water or 0.9 per cent. salt solution after which one part of normal sodium hydrate solution is added and the mixture again boiled. The appearance of a flocculent precipitate within two hours is considered by Noguchi as diagnostic of general paresis. Blood-free fluid must be used. All spinal fluid contains globulin and in normal fluids or fluid from cases other than general paresis a flocculent precipitate may be obtained nearly always either by reboiling once or twice or allowing the

1. Thirty-First Ann. Rep. Binghamton State Hospital, Binghamton, N. Y., 1910, J. B. Lyon Co., Albany, p. 31.

mixture to stand for twenty-four hours. Usually boiling for a second or third time after the fluid has once cooled without allowing the fluid to stand, will bring down a flocculent precipitate in cases which show no evidences of general paresis.

Positive results were obtained by one or the other of these methods in twenty-seven out of twenty-nine non-paretic cases. In some of these fluids the precipitate occurred as quickly as in general paresis and after one heating only. Reference to Table 2 will show that sixteen out of twenty-nine non-paretic cases, 55 per cent. of the total, gave positive results with the butyric acid reaction when the technic of Noguchi was employed. Rosanoff and Wiseman[2] in psychoses other than general paresis, obtained positive results with the butyric acid method in 10.8 per cent. and doubtful reactions in 7.2 per cent. of the 333 cases, making a total of 18 per cent. which failed to give definite negative reactions. The technic of Noguchi was followed in these tests.

Dr. F. W. Mott,[3] F.R.C.P., London, F.R.S., pathologist to the London County Asylums, in his Oliver-Sharpey lectures on the cerebrospinal fluid delivered before the Royal College of Physicians of London on April 22 and 29, 1910, says of the butyric acid reaction of Noguchi: "I have applied this test to a considerable number of fluids, and have obtained a positive reaction in many non-specific cases, in fact, in all cases of dementia, whether non-specific or specific, and have found that the amount of precipitate is proportional to the degree of degeneration of nervous tissue, being most marked in the progressive degeneration of general paralysis of the insane."

Attention was called to the fallacy of this reaction in the last annual report of the Binghamton State Hospital[4] and also to the fact that it could be easily demonstrated by using larger amounts of the various reagents concerned than are recommended by Noguchi,[5] preserving, however, the same proportions (0.5 c.c. of spinal fluid, 2.5 c.c. of the 10 per cent. butyric acid solution and 0.5 c.c. of normal sodium hydrate instead of 0.1 c.c. of spinal fluid, 0.5 c.c. of 10 per cent. butyric acid and 0.1 c.c. of normal sodium hydroxid). "It is entirely to one's individual taste whether one or a multiple of the quantities indicated above will have to be employed."

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2. Rosanoff, A. J., and Wiseman, J. I.: Syphilis in Insanity, Am. Jour. Insan., 1910, lxvi, 430.

3. Mott, F. W.: Oliver-Sharpey Lectures on the Cerebrospinal Fluid, Lancet, London, 1910, ii, 79.

4. Thirty-First Ann. Rep. Binghamton State Hospital, p. 32.

5. Noguchi, H.: Relation of Protein, Lipoids, and Salts to the Wassermann Reaction, Jour. Exper. Med., 1909, ii, 92.

W. H. Hough[6] of Washington, D. C., says of the butyric acid reaction:

> I found it positive, and in some instances very pronounced, in a number of cases of arteriosclerotic dementia where no evidence of syphilitic or inflammatory disease could be found, either in the cytology of the fluid or in the histological examination of the nervous system in the cases in which autopsy could be performed. It may be mentioned also that a large majority of the post-mortem fluids from non-inflammatory cases showed a positive butyric acid reaction.

He reports positive results in 48 per cent. of his non-paretic cases and obtained five positive results in seven post-mortem fluids. He followed the technic of Noguchi throughout. It is beyond dispute that there is an increase of the globulin content in the spinal fluid in cases of general paresis, although it occurs in other psychoses as well and is not absolutely diagnostic of that disease.[7]

The demonstration of an increase in the globulin content suggested the Nonne-Jones reaction, which has also been spoken of as valuable in the diagnosis of general paresis. This reaction consists in the formation of a white ring such as is obtained in Heller's test for albumin on bringing spinal fluid in contact with a saturated solution of neutral ammonium sulphate solution in a pipette. In the laboratory of the Binghamton State Hospital we have obtained positive results uniformly in general paresis but have had the same experience as shown in Table 2 with the spinal fluid in other psychoses. If a white ring does not form immediately at the point of contact, it will form almost always after standing for a short time. When there is any doubt as to the result a larger amount of fluid can be used and the reaction performed in a test-tube. Positive results will be obtained in this manner from practically all spinal fluids. In this, as in all of the contact tests, a more decided reaction is, however, obtained in general paresis. No reference is made here to the results obtained by the so-called precipitate reactions with lecithin and the taurocholate and glycocholate of sodium, owing to the fact that these reactions have already been shown to be unreliable.[4]

One of the most valuable of the laboratory methods of diagnosis of general paresis consists in the demonstration of a lymphocytosis in the spinal fluid. The method probably most often used is the old method of Widal and Ravaut, that of centrifuging the fluid and examining the sediment for an increase in the number of lymphocytes. This is an easy and fairly accurate method. We have found, however, that a moderate

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6. Hough, W. H.: Remarks on the Comparative Diagnostic Value of the Noguchi Butyric Acid Reaction and Cytological Examination of the Cerebrospinal Fluid, Bull. 2, Government Hospital for the Insane, Washington, D. C., 1910, p. 122.

7. May, J. V.: A Review of the Recent Studies of General Paresis, 1909. Tr. Am. Med. Psychol. Assn., Lord Baltimore Press, Baltimore, Md., xvi, 337.

increase of lymphocytes will occasionally be overlooked. Much more reliable is the accurate estimation of the number of cells per cubic millimeter of fluid by means of the Fuchs-Rosenthal counting chamber. In this method the pipette usually employed in counting the white blood cells is used.

The following mixture is usually employed for staining the white and dissolving the red cells: Methyl violet 0.2, glacial acetic acid 4, water 100. Fill the pipette with stain to the point marked 1 and then fill to the point marked 11 with cerebrospinal fluid, uncentrifuged. Shake thoroughly, let stand for five minutes and count by means of the Fuchs-Rosenthal counting chamber. The ruled surface of the cell contains 3.2 cubic mm. of the fluid. Count all of the white cells in the entire ruled area of the slide, multiply by 11 and divide by 32. The result is the number of cells per cubic millimeter.

As the chamber is 0.2 mm. deep the source of error can be entirely disregarded.

This method requires a very short time, after a little experience, and is quite reliable. The stain can be greatly improved by increasing the amount of glacial acetic acid used. Polychrome methylene-blue is recommended by Cornell. The spinal fluid should be free from blood, although a small amount does not materially affect the result. Reference to Table 2 will show that in twenty-five out of twenty-eight of the non-paretic cases there were five cells or less per cubic millimeter. On the other hand, in the forty cases of general paresis in which cell counts were made as shown in Table 1, only one case showed less than five cells to the cubic millimeter, while eight cases showed from five to twenty-five cells, twelve cases from twenty-five to fifty cells, fourteen cases from fifty to 100 cells, two cases from 100 to 200 cells, and three cases over 200 cells, per cubic millimeter. In our hands this method has constituted the most reliable laboratory procedure available in the diagnosis of general paresis. It will frequently show a considerable increase in the number of cells when the Widal-Ravaut method gives negative results.

Whenever a lymphocytosis is shown, a differential count of the cells should be made by the Alzheimer method, as follows:

Mix five c.c. of the spinal fluid with 10 c.c. of 95 per cent. alcohol and centrifuge for one hour. Pour off the alcohol and replace by absolute alcohol. After standing for one hour replace by equal parts of absolute alcohol and xylene followed by xylene for one hour and imbed the sediment in paraffin by the usual process. Sections should be at least 12 microns thick and stained by 1 per cent. toluidin blue and by the Unna-Pappenheim stain. At least 100 cells should be counted and the percentage of lymphocytes, polynuclears, large mononuclears, macrophages, *Körnchenzellen*, plasma cells, endothelial cells, etc., carefully estimated.

There will usually be found to be about 80 per cent. of lymphocytes and from 1 to 5 per cent. of plasma cells, with varying percentages of the other elements in cases of general paresis. The great increase of phagocytic cells and *Körnchenzellen* or fatty granule cells in all post-

TABLE 1.—GENERAL PARESIS

Case No.	General Characteristics.*		Cerebrospinal Fluid.									Blood Serum.	
			Estimation of Globulin and other Proteins.					Sugar Determination.	Estimation of Cellular Elements.		Test for Antibodies.	Tests for Antibodies.	
	Appearance.	Pressure.	Nitric Acid Contact Test.	Nitro-Magnesium Contact Test.	Esbach Albuminometer, Per Cent.	Nonne-Jones Contact Test.	Butyric Acid Test.	Fehling Qualitative Test.	Widal Method.	Fuchs-Rosenthal Cell Count Meth.	Noguchi-Wassermann Reaction.	Noguchi-Wassermann Reaction.	Wassermann Reaction.
1	†	>	+	+	.3	+	+	+	+	...	+	+	...
2	†	>	+	+	.15	+	+	+	+	...	+	+	+
3	†	>	+	+	.09	+	+	+	+	272	+	+	...
4	†	>	+	+	.12	+	+	+	+	36	+	+	+
5	†	>	+	+	.07	+	+	+	—	4	+	+	+
6	†	>	+	+	.12	+	+	+	+	...	+	+	...
7	†	>	+	+	.15	+	+	+	+	32	+	+	+
8	†	>	+	+	.07	+	+	+	+	...	+	+	...
9	†	>	+	+	.12	+	+	+	+	...	+	+	...
10	†	>	+	+	.21	+	+	+	+	8	+	+	+
11	†	>	+	+	.12	+	+	+	+	...	+	+	...
12	†	>	+	+	.12	+	+	+	+	...	+	+	...
13	†	>	+	+	.09	+	+	+	+	89	+	+	...
14	†	>	+	+	.12	+	+	+	+	...	+	+	...
15	†	>	+	+	.04	+	+	+	+	93	—	+	+
16	†	>	+	+	.12	+	+	+	+	273	+	+	+
17	†	>	+	+	.21	+	+	+	+	32	+	+	...
18	†	>	+	+	.12	+	+	+	+	...	+	+	...
19	†	>	+	+	.06	+	+	+	+	9	—	+	+
20	†	>	+	+	.09	+	+	+	+	54	+	+	...
21	†	>	+	+	.12	+	+	+	+	30	+	+	+
22	†	>	+	+	.04	+	+	+	+	...	+	+	+
23	†	>	+	+	.06	+	+	+	—	35	+	+	—
24	†	>	+	+	.09	+	+	+	+	...	+	+	...
25	†	>	+	+	.12	+	+	+	+	...	+	+	...
26	†	>	+	+	.18	+	+	+	+	89	+	+	+
27	†	>	+	+	.07	+	+	+	+	68	+	+	...
28	†	>	+	+	.12	+	+	+	+	...	+	+	...
29	‡	>	+	+	.09	+	+	+	+	...	+	+	+
30	‡	>	+	+	.18	+	+	+	+	...	+	+	...
31	†	>	+	+	.07	+	+	+	—	...	+	+	+
32	†	>	+	+	.09	+	+	+	...	...	+	+	+
33	†	>	+	+	.15	+	+	+	+	203	+	+	+
34	†	>	+	+	.15	+	+	+	+	36	+	+	+
35	†	>	+	+	.25	+	+	+	+	46	+	+	+
36	†	>	+	+	.12	+	+	+	+	30	+	+	+
37	†	>	+	+	.12	+	+	+	+	61	+	+	+
38	†	>	+	+	.06	+	+	+	+	19	—	+	+
39	†	>	+	+	.12	+	+	+	+	39	+	+	+
40	†	>	+	+	.12	+	+	+	+	66	+	+	+
41	†	>	+	+	.09	+	+	+	+	108	+	+	+
42	†	>	+	+	.06	+	+	+	+	65	+	+	+
43	†	>	+	+	.09	+	+	+	+	22	+	+	+
44	†	>	+	+	.06	+	+	+	+	20	—	+	+
45	†	>	+	+	.12	+	+	+	+	42	+	+	+
46	†	>	+	+	.06	+	+	+	—	80	+	+	+
47	†	>	+	+	.12	+	+	+	+	27	+	+	+
48	†	>	+	+	.06	+	+	+	+	7	+	+	+
49	†	>	+	+	.04	+	+	+	—	46	+	+	+
50	†	>	+	+	.03	+	+	+	—	22	+	+	+
51	†	>	+	+	.06	+	+	+	—	69	—	+	+
52	†	>	+	+	.09	—	+	+	+	95	+	+	+
53	†	>	+	+	.09	—	+	+	+	56	—	+	+
54	†	>	+	+	.06	—	+	+	+	18	+	+	+
55	†	>	+	+	.15	+	+	+	+	72	+	+	+
56	†	>	+	+	.09	+	+	+	+	118	+	+	—
57	†	>	+	+	.12	+	+	+	+	84	+	+	+

* Reaction alkaline throughout.
† Clear. ‡ Cloudy < Decreased. > Increased. = Normal.

mortem fluids is of considerable interest. A lymphocytosis is not of course absolutely diagnostic of general paresis and occurs in cerebrospinal syphilis as well as in some cases of locomotor ataxia and tubercular meningitis.

TABLE 2.—PSYCHOSES OTHER THAN GENERAL PARESIS

Case Number.	Cerebrospinal Fluid.										Blood Serum.		Diagnosis Form of Psychosis.	Deterioration.	History of Syphilis.
	General Characteristics.*	Estimation of Globulin and other Proteins.					Sugar Determination.	Estimation of Cellular Elements.		Test for Antibodies.	Test for Antibodies.				
	Pressure.	Nitric Acid Contact Test.	Nitro-Magnesium Contact Test.	Esbach Albuminometer. Per Cent.	Nonne-Jones Contact Test.	Butyric Acid Test.	Fehling Qualitative Test.	Widal Method.	Fuchs-Rosenthal Cell Count Meth.	Noguchi-Wassermann Reaction.	Noguchi-Wassermann Reaction.	Wassermann Reaction.			
1	<	+	+	.03	+	—	—	—	1	—	—	—	Dementia præcox...	Advanced.	—
2	<	+	+	.06	+	—	+	—	6	—	—	—	Alcoholic psychosis.	Slight....	+
3	<	+	+	.09	+	+	+	—	5	—	+	—	Locomotor ataxia...	Slight....	+
4	<	+	+	.04	+	—	+	—	1	—	—	..	Glioma of brain....	Advanced.	—
5	<	+	+	.07	+	—	+	—	3	—	+	+	Locomotor ataxia...	Advanced.	—
6	<	+	+	.05	+	+	+	—	3	—	—	—	Dementia præcox...	Advanced.	—
7	<	+	+	.06	+	+	—	—	3	—	—	—	Dementia præcox...	Advanced.	—
8	<	+	+	.03	+	—	+	—	1	—	—	—	Dementia præcox...	Advanced.	—
9	<	+	+	.03	+	+	+	—	0	—	—	—	Dementia præcox...	Advanced.	—
10	<	+	+	.12	+	+	+	—	2	—	+	—	Dementia præcox...	Advanced.	—
11	<	+	+	.05	+	—	+	—	2	—	+	+	Dementia præcox...	Advanced.	—
12	<	+	+	.06	+	+	—	—	2	—	—	—	Dementia præcox...	Advanced.	—
13	<	+	+	.06	+	—	+	—	1	—	—	—	Dementia præcox...	Advanced.	—
14	<	+	+	.06	+	+	+	—	3	—	+	—	Dementia præcox...	Advanced.	—
15	<	+	+	.12	+	—	+	—	6	—	+	—	Dementia præcox...	Advanced.	—
16	<	+	+	.04	+	—	+	—	3	—	+	+	Dementia præcox...	Advanced.	—
17	<	+	+	.05	+	—	+	—	3	—	—	—	Dementia præcox...	Advanced.	—
18	<	+	+	.05	+	+	+	—	1	—	—	—	Dementia præcox...	Advanced.	—
19	<	+	+	.05	+	—	+	—	3	—	—	—	Dementia præcox...	Advanced.	—
20	<	+	+	.06	+	—	+	—	3	—	+	—	Dementia præcox...	Advanced.	—
21	<	+	+	.06	+	+	+	—	1	—	—	—	Dementia præcox...	Advanced.	—
22	<	+	+	.03	+	+	+	—	2	—	—	—	Dementia præcox...	Advanced.	—
23	<	+	+	.06	+	+	+	—	1	—	—	—	Dementia præcox...	Advanced.	—
24	<	+	+	.09	+	—	+	—	2	—	—	—	Dementia præcox...	Advanced.	—
25	<	+	+	.09	+	+	+	—	2	—	—	—	Dementia præcox...	Advanced.	—
26	<	+	+	.05	+	+	+	—	2	—	—	—	Dementia præcox...	Advanced.	—
27	<	+	+	.06	+	+	+	—	2	—	—	—	Dementia præcox...	Advanced.	—
28	<	+	+	.06	+	—	+	—	3	—	+	—	Unclassified.....	Slight....	—
29	<	+	+	.09	+	—	+	—	5	—	+	—	Unclassified.....	Slight....	+

* Appearance clear and reaction alkaline throughout.
< Decreased. > Increased. = Normal.

The Noguchi modification of the Wassermann reaction was used in the cerebrospinal fluid and in the blood-serum in both series of cases. In fifty-seven cases of general paresis the Noguchi method gave fifty-one positive reactions in the spinal fluid. In the other psychoses it gave only one positive in twenty-nine cases and that in a case of locomotor ataxia. In the blood-serum the Noguchi-Wassermann method gave positive reactions in all of the fifty-seven cases of general paresis, while in the twenty-nine cases of other psychoses it gave ten positive results. Of these ten cases two were cases of locomotor ataxia and one had a history of syphilis. In the other seven cases no history is available. The original Wassermann

reaction in the blood-serum of the general paresis cases gave thirty-eight positive results in forty cases and in the non-paralytic cases gave twenty-five negatives out of twenty-eight. Of the three positive reactions one was a case of locomotor ataxia. No reason can be assigned for the other two reactions. Both of these, however, were cases in which there was a reaction to the Noguchi modification. In comparing the two systems the Noguchi modification is by many looked on as being too sensitive and giving too many positive results in non-specific cases. This, however, as Noguchi suggests, may be due to the use of excessive amounts of antigen. In regard to the interpretation of results Noguchi[8] says:

> If there is a faint degree of hemolysis, the main bulk of corpuscles being intact, the reaction should be called positive. A more intense hemolysis, with about 10 to 20 per cent. dissolution of the corpuscle mass, should be called weakly positive, while 30 to 40 per cent. hemolysis is designated as faintly positive. Neither the weakly positive nor the faintly positive reaction should be accepted as a definite diagnosis of syphilis without the presence of strong clinical evidence in favor of such a diagnosis.

In another place he says:[9]

> It is my rule to base the diagnosis of syphilis on unmistakably strong reactions only, but never on weak reactions when the clinical diagnosis is unknown. On the other hand, I take even a faint positive reaction as a sign of active syphilitic process still present when the specimen is derived from a known luetic case. Again, for the purpose of excluding possibility of syphilis from a case I put value even on a faint reaction, no matter whether the person may seem healthy or not.

It will thus be seen that the result obtained is interpreted differently, depending on whether the case is one of known or probable syphilis, one showing no evidence or history of syphilis or one of which nothing is known unless there is practically a complete inhibition of hemolysis which does not always occur in many known syphilitic cases. In this way the personal equation enters strongly into the results obtained and the least inaccuracy in the amounts of the various factors concerned materially changes the results. The most serious objection to the Noguchi modification would appear to be the variability in the amount of specific amboceptor contained in the capillary drop of blood-serum used. No two capillary drops from any two different tubes are the same. Negative results will sometimes be obtained from a capillary drop of blood-serum which will give positive results when from 0.02 to 0.04 c.c. are accurately measured from a graduated pipette for the test. According to Noguchi a capillary drop contains 0.02 c.c. of blood-serum. Measuring a few drops from different capillary tubes will readily convince anyone that

8. Noguchi: Serum Diagnosis of Syphilis, First Edition 1910, p. 61.

9. Noguchi, H.: Discussion of Serodiagnosis of Syphilis, Jour. Am. Med. Assn., 1909, liii, 1541.

this is only occasionally true. Blowing out a few drops on a glass slide from capillary pipettes made from several different sizes of glass tubing will be sufficient to convince anyone that this is a very indefinite amount.

We have obtained very satisfactory results here from the use of the original Wassermann reaction. This method has the advantage of using a definite and easily and accurately measured amount of serum. It is quite unusual for blood to contain a sufficient amount of natural antisheep amboceptor to influence the result. Complement is completely removed by inactivation. We have not found the paper preparations of Noguchi to be stable or reliable for more than a few months although they are much more convenient to use than the liquid antigen and amboceptor. The amount of complement contained in guinea-pig serum is extremely variable and sometimes leads to erroneous conclusions. Only full-grown pigs should be used and a titration of the complement in the serum from a number of guinea-pigs will show that there is no absolutely invariable dose which can be depended on for use. We have found the following method of using the Wassermann reaction very satisfactory:

Patient's serum 0.2 c.c. or 0.1 c.c. (inactivated at 56 C. for one-half hour) plus 1 unit of antigen, plus 0.1 c.c. of guinea-pig complement undiluted, plus 2 c.c. of 0.85 per cent. salt solution. Incubate for one hour at 37 C. Add 1 c.c. of a 5 per cent. suspension of sheep corpuscles and 2 units of anti-sheep amboceptor. Incubate for two hours using the customary positive and negative controls.

The acetone-insoluble fraction of the alcoholic extract of human heart is used in the paper form. The antisheep amboceptor is also used in the paper form and both of these have been as satisfactory as the paper preparations used in the Noguchi modification.

An effort has been made to adopt the "meiostagmin" reaction of Ascoli to the diagnosis of general paresis by using the cerebrospinal fluid and the alcoholic extract of human heart as antigen. Ascoli announced[10] that the addition of antigen of syphilis in varying dilutions to the serum of a person suffering from that disease brought about a considerable change in the surface tension of the fluid on standing for a time in the incubator. This change in tension is measured by a Traube stalagmometer. After numerous attempts we have been unable to obtain any uniform results with the serum of syphilitic cases.

CONCLUSIONS

1. There is an increase in the protein content of the cerebrospinal fluid in general paresis.

2. There is a marked increase in the globulin content in general paresis.

10. Ascoli, M.: Die Spezifische Meiostagminreaktion, Münch. Med. Wchnschr., 1910, lvii, 63.

3. There is an increase in the globulin content in psychoses other than general paresis in many cases.

4. The increase in the globulin content can be shown better by using larger quantities of the reagents suggested by Noguchi for his butyric acid test, preserving, however, the same proportions. This method will show an increase which would often be overlooked otherwise.

5. The butyric acid test of Noguchi has not been accepted as absolutely diagnostic of general paresis.

6. The demonstration of a lymphocytosis in the spinal fluid is one of the most reliable laboratory methods in the diagnosis of general paresis.

7. In the performance of the Noguchi modification of the Wassermann reaction it is important to use a sufficient quantity of the serum to be tested, the capillary drop recommended by Noguchi being a very variable amount.

8. The Noguchi method of interpreting the results of the Wassermann test differs largely from that of many other laboratory workers and may lead to various conclusions, depending on the observer.

9. The original Wassermann method is to be preferred to the Noguchi modification.

10. The Noguchi method of using antigen and amboceptor in the paper form can be adapted to the original Wassermann reaction with advantage.

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EDEMA OF THE PIA-ARACHNOID

ITS NATURE, SIGNIFICANCE, RELATIONSHIP TO AND ASSOCIATION WITH DISEASE PROCESSES *

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INTRODUCTION

The following article is a study of the nature and significance of fluid accumulations within the subarachnoid space, based principally on post-mortem observations and mechanical considerations.

For the sake of brevity it may be stated at the outset that the terminology employed to designate the various conditions of the brain and its membranes associated with excessive fluid accumulations has been confused by the use of many names, employed without due consideration of the etiological or mechanical factors involved. It is therefore necessary to describe the various anatomical findings to which these different terms have been applied.

1. Pial Edema; Edema of the Pia Mater; Edema of the Pia Arachnoid; Cerebral Edema; Wet-Brain.—These terms have been employed indefinitely to designate conditions accompanied by excess of fluid in the pia-arachnoid. The brain on cut section may or may not appear to be moist; the ventricles may or may not be "dilated." The volume of the brain is not increased, on the contrary it often has given the impression of having been compressed. It is this picture which is generally associated with and attributed to chronic alcoholism, and which in this country has often been referred to as wet-brain.

2. Cerebral Edema; Edema of the Brain.—Swelling of the brain with increase in its volume. The pia-arachnoid may or may not have contained an excess of fluid; usually the convolutions are described as flattened, owing, as supposed, to pressure of the voluminous brain against the skull. These brains are then described as being moist, the condition being usually attributed to transudation into the brain substance of serum from the blood-vessels.

3. Serous Meningitis.—Described usually as a serous or exudative inflammation of the soft meninges, with exudate into the subarachnoid space and its prolongations, with or without gross thickenings of the

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*From the Pathological Laboratories of Bellevue Hospital, Dr. Charles Norris, Director.

meninges. The ventricles may or may not be dilated and the brain is or is not secondarily involved, the seat of an edematous or inflammatory process. Certain writers in this country, notably Dana, have regarded "alcoholic wet-brain" and serous meningitis as synonymous.

4. Hydrops ex Vacuo.—This term has been used to describe the accumulation of fluid following the shrinkage of the brain from old age or from various pathological causes, to be mentioned later.

5. Chronic External Hydrocephalus.—This term has been used to describe those appearances already referred to above; by some authors, also, to describe accumulations of fluid in the subdural space and even those found between the calvarium and the dura mater.[1]

The above summary, derived from a critical survey of the literature, shows that these various terms, although in themselves perfectly clear and descriptive, have been used indiscriminately to designate different anatomical conditions without any consideration of the underlying pathological processes in which they had their origin.

Although the older writers did not formulate any noteworthy theories as to the causation of excessive accumulations of fluid in the brain,[2] they nevertheless displayed considerable interest in its supposed mechanical effects. Thus we find in Watson's Lectures[3] (1845), the following rather quaint description of fluid collections in the pia-arachnoid in connection with uremic coma.

> Now when death had thus taken place in the way of coma and the case had been complicated with anasarca, and serous liquid is found accumulated in unnatural measure in the cerebral ventricles, and in the tissue of the pia mater, it seems reasonable to ascribe the coma to the presence and the pressure of that liquid. The dropsy has extended to the brain. And this view of the matter is strengthened by the connection which may sometimes be noticed between the accession of the coma and the visible increase of the dropsy in other parts of the body. My own experience accords entirely with that of Dr. Christison as expressed in the following statement: "If the dropsical fluid be allowed greatly to accumulate, drowsiness, the first symptom of the affection of the head, very soon makes its appearance in the generality of cases and it will speedily pass to fatal coma if not controlled, but the removal of the dropsy will usually remove the drowsiness." To many cases, however, this explanation will not apply, there being no morbid collection of water within the skull, nor any other appreciable change there; nor perhaps, any dropsy elsewhere.

The fluid collections described by Watson were doubtless that very common form of pial effusion with which this paper particularly has to do.

In 1861, Traube[4] opened up a new vista in the field of intracranial mechanics by stating that the brain is often swollen and edematous in

1. Riva, E.: Idrocephalo interno ed esterno, Riv. sper di freniat, 1908, xxxiv, 207.

2. Traube quotes Osborne as attributing the condition to an arachnitis.

3. Watson, Thomas: Principles and Practice of Physics, London, 1845.

4. Traube, L.: Eine Hypothese über den Zusammenhang, in welchem die sogenannten urämischen Anfälle zur Erkrankung der Nieren stehen, Allg. med. Centr.-Ztg., 1861, xxx, 818.

certain cases of uremia. Since Traube[5] may thus be regarded as the founder of a new school, a somewhat detailed consideration of his paper is imperative. In discussing uremia he says: "In all cases observed by me in which a careful examination of the cranial contents has been made after death, there was observed with a well-marked anemia [*Blut-Armuth*] of the brain, a more or less considerable edematous swelling of the same (as shown by flattening of the brain convolutions and dryness of the arachnoid, with moist glistening of the cut section)."[6] Further on he writes: "In some of these cases the fresh petechiæ [*Blut-Ergüsse*] were distributed in the form of fine sand up to hemp-seed foci through the large and small brain and pons due," as he states, "to increased arterial pressure."[7] He lays especial stress upon two factors in the causation of brain edema in uremia; first, the hydremic condition of the blood, due to loss of albumin through the urine and through gastro-intestinal catarrh, and second, to the increased tension in the aortic system from hypertrophy of the left ventricle.[5] He goes on to say:

> If through any accidental cause there occurs a sudden increase of blood-pressure, or if there is a sudden diminution in the thickness of the blood-serum, there transudes a serous fluid through the walls of the small arteries into the brain substance, and thus brain edema ensues. The fluid elements of the blood transude under the mean pressure in the aortic system. Since this pressure is greater than that in the capillaries and veins, so these vessels must finally be compressed. The necessary consequence of a brain edema arising from such a cause is an *anemia of the brain substance*. The transudation, as will be readily understood, resists up to the moment when the tension of the edematous brain parts equals the mean tension of the aortic system.

Traube's explanation of the causes bringing about transudation is not generally accepted. He cites a case of cerebral edema in an epileptic who at autopsy was found to have a cysto-sarcoma of the brain. There is reason to believe that from this case he derived the idea on which he founded his theory as to the causation of the attacks of coma and convulsions occurring in cases of uremia and of chronic lead-poisoning.

Several years after Traube's paper appeared, Billroth[8] (1869) observed anatomical changes in the brains of postoperative subjects somewhat similar to those described by Traube.

Niemeyer[9] (1877) and Huguenin [10] (1878) reconsidered the problem chiefly in connection with the phenomena of uremia.

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5. Traube, L.: Gesammelte Beiträge zur Pathologie und Physiologie, ii, Part 1, 551.

6. Traube, L.: Gesammelte Beiträge zur Pathologie und Physiologie, ii, Part 1, p. 553.

7. Traube, L.: Gesammelte Beiträge zur Pathologie und Physiologie, ii, Part 1, p. 554.

8. Billroth: Ueber akute Mening. serosa und akute Gehirnödem nach chirurgischen Operationen. Wien. med. Wchnschr., 1869, xix, 2.

9. Niemeyer: Lehrbuch der speziellen Pathologie und Therapie. Ed. 9, 1877, ii.

10. Hugenin, G.: Hydrocephalus und Oedem des Hirns, Handbuch der speziellen Pathologie und Therapie von v. Ziemssen, Suppl. Vol., 1878, p. 25.

Bergmann[11] (1880) described an edematous condition in connection with injuries of the brain, while Dean[12] produced local edema experimentally by placing a glass disc between the brain and the dura.

Phelps[13] (1897) believes that edema of the brain may follow on contusion and W. N. Bullard[14] (1895) states that edema of the brain results from concussion. The latter writes:

> Brain swelling undoubtedly occurs in certain cases of apoplexy, and in a chronic form in many intracranial diseases. This, or something analogous to it, the so-called acute edema of the brain, is the immediate cause of death in cases of acute alcoholism, of sunstroke and perhaps (in its chronic form) in uremia.

Walton and Brooks[16] (1897) have also dwelt on the subject of edema of the brain and its membranes from a surgical standpoint. Walton in his subsequent paper[17] has considerably modified his previous conceptions.

W. B. Cannon[18] in an article published in 1901, presented certain striking and original conclusions on the causation of cerebral edema following trauma, which will be later referred to, while at about the same time Mott[19] succeeded in producing experimental edema of the brain in dogs by ligation of arteries, and Osler[20] (1901), following Traube, described cerebral edema particularly in connection with uremic coma.

The subject of cerebral edema has aroused great attention among physiologists only within a comparatively recent period. Wilson[21] (1904) studied the condition in connection with uremic and eclamptic seizures.

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11. Bergmann: Die Lehre von den Kopfverletzungen, Deutsch. Chir., Stuttgart, 1880, xxx, 420.
12. Dean, H. P.: Cerebrospinal Pressure, Jour. Path. and Bacteriol., 1893, I, 26.
13. Phelps, C.: Traumatic Injuries of the Brain and Its Membranes, New York, 1897, p. 53.
14. Bullard, W. N.: A Consideration of Some of the Indications for Operation in Head Injuries, Med. and Surg. Rep., City Hosp., Boston, Series 6, 1895, p. 60.
15. Bullard, W. N.: Increase of Intradural Pressure in Head Injuries, Boston Med. and Surg. Jour., 1898, cxxxviii, 271.
16. Walton, G. L., and Brooks, W. A.: Observations on Brain Surgery Suggested by a Case of Multiple Cerebral Hemorrhage, Boston Med. and Surg. Jour., 1897, cxxxvi, 301.
17. Walton, G. L.: Subarachnoid Serous Exudation Productive of Pressure Symptoms after Head Injuries, Am. Jour. Med. Sc., 1898, cxvi, 267.
18. Cannon, W. B.: Cerebral Pressure Following Trauma, Am. Jour. Physiol., 1901, vi, 91.
19. Mott, F. W.: Preliminary Communication on the Changes in the Brain, Spinal Cord, Muscles and Other Organs Found in Persons Dying after Prolonged Epileptiform Convulsions, Arch. Neurol., London, i, 493.
20. Osler, Wm.: Practice of Medicine, 1901, p. 997.
21. Willson, R. N.: The Pathogenesis of Uremia and Eclampsia, Jour. Am. Med. Assn., 1904, xliii, 1019.

B. Bramwell[22] (1906) mentioned cerebral edema as a possible cause of uremic attacks. The following year A. E. Russell[23] (1907) introduced his thesis in the following terms: "The purpose of this paper is to put forward the proposition that there is evidence to show that the cerebral manifestations of uremia are dependent on cerebral anemia produced by an increase in intracranial tension resulting from cerebral edema." Following Russell, Cushing and Bordly[24] (1908) published a paper based chiefly upon the observations and findings ante and post mortem in a case of uremia in which decompression was performed, as a result of which he concludes: "In regard to uremia, therefore, to be conservative we may at least say that the symptoms are elicited by edema resulting from some toxic agency, and are not, as is commonly supposed, due to the direct effect on the cerebral tissues of the toxic agent alone."[25]

Russell[26] has very recently (1909) presented additional evidence supporting the hypothesis that the presence of edema of the brain is an important factor in the production of uremic phenomena. He says, speaking of Cushing's decompression case (mentioned above) and other recent data:

> The foregoing facts indicate that in uremia a state of increased intracranial tension is present, and that relief of pressure by lumbar puncture or decompression causes a marked alleviation of the symptoms. Traube's view that cerebral edema (which would produce the rise in the intracranial tension) produces anemia of the brain is strongly supported by the above facts and especially by the striking case of decompression.

Russell does not deny a concomitant toxic action on the brain but thinks it possible that status epilepticus may be due to an anemia of the brain following on a prolonged increase of intracranial pressure. There is, as has been shown, a very strong tendency among the members of the Traube school to assume that the rise in intracranial tension is due to cerebral edema. As a matter of fact cerebral edema is a very inconsistent phenomenon in uremia, as has been noted not only by Russell but by Bramwell, and by a large number of authors who are not identified with

22. Bramwell, B.: Clinical Lecture on Uremia and its Treatment, Clinical Studies, Edinburgh, 1906, Part 1, p. 1.

23. Russell, A. E.: Uremia, West. Lond. Med. Jour., 1907, xii, 9. This paper contains an excellent bibliography of the use of lumbar puncture in uremia.

24. Cushing, H., and Bordley, J., Jr.: Subtemporal Decompression in a Case of Chronic Nephritis with Uremia, etc., Am. Jour. Med. Sc., 1908, cxxxvi, 484.

25. Cushing has dealt with the subject to a less extent in previous papers. See Am. Jour. Med. Sc., 1903, cxxv, 1017.

26. Russell, A. E.: The Gouldstonian Lectures on Some Disorders of the Cerebral Circulation and Their Clinical Manifestations, Lancet, London, 1909, I, 963, 1031, 1093.

27. Huguenin, Ibid.

the Traube school, namely, Huguenin, John Rose Bradford,[28] Senator[29] and Riesman.[30]

In this connection the observations of Kolisko[31] on swollen and edematous brains, are most interesting. This observer has described a type of brain in which the brain is swollen and wet, the ventricles reduced in size and the fluid of the subarachnoid space diminished or absent, the convolutions flattened, associated with dural hernias, and marked *impressiones digitates*—the latter being due to a compression atrophy of the inner table of the skull described as following upon a premature ossification of the cranial sutures.

The clinical phenomena in these cases have not appeared to bear much resemblance to those recorded by the Traube school.

The term "serous meningitis," the etiological and anatomical status of which is intimately involved in any consideration of sub-arachnoid effusions, is of comparatively recent introduction, although its employment antedates the bacterial era of medicine.

Since the development of our subject depends chiefly on anatomical rather than general clinical considerations, we shall regard serous meningitis chiefly from the anatomical and mechanical point of view, and limit our review of it.

Among earlier writers it was usual to ascribe all cases of internal and external hydrocephalus to tuberculous meningitis, although certain observers, notable among whom were Dietl,[32] Rokitansky,[33] Wunderlich[34] and Leubuscher[35] did not agree with this opinion.

In 1869 Billroth[35] distinguished a form of acute hydrocephalus of supposed non-tuberculous origin to which he applied the name of meningitis serosa. But it was not until Eichorst[36] (1887) published his observations that much emphasis was laid on the idea that a simple serous inflammation was the pathological process in many of these cases.

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28. Bradford, John Rose: Observations on the Pathology of the Kidneys. Gouldstonian Lectures, Lancet, London, 1898, i, 917.

29. Senator: Diseases of the Kidneys, Nothnagel's Encyclopedia, Am. Ed., p. 103.

30. An analysis of the fourteen autopsies on cases of uremic aphasia, quoted by Dr. D. Riesman, Uremic Aphasia, Jour. Am. Med. Assn., 1902, xxxix, 883, shows six in which there was moisture of the brain or edema. One had marked distention of the right ventricle and the remaining seven brains were described as normal.

31. Kolisko, Alexander: Plötzlicher Tod aus natürlicher Ursache, Handbuch der ärztlichen sachverständigen Tätigkeit. Vienna and Leipsic, 1906, ii, 702 et seq.

32. Dietl: Anatomischer Klinik der Gehirnkrankheiten, 1846.

33. Rokitansky: Lehrbuch der pathologischen Anatomie, 1856, ii, Ed. 2.

34. Wunderlich: Die Pathologie und Therapie, 1854, iii, Ed. 2.

35. Leubuscher: Die Pathologie und Therapie der Gehirnkrankheiten, Berlin, 1854.

36. Eichorst: Handbuch der speziellen Pathologie und Therapie, 1887, iii.

Eichorst believed that the process was due to a mild infection and remained serous throughout, while Gowers[37] (1892) described the process as a meningitis simplex as distinguished from a meningitis purulenta. He was followed shortly by Quincke[38] who elaborated a definite symptomatology for this disease.

The literature of serous meningitis has become so enormous that it is out of the question to attempt to review it, especially since Boenninghaus[39] has given a comprehensive summary of the subject up to 1897 and Hafslauer[40] has subsequently reviewed it up to 1906.

The subject did not receive much attention in the United States until Dana[41] (1897) published his article entitled "Acute Serous Meningitis (Alcoholic Meningitis, Wet-Brain)." Since then, articles, monographs or reports of cases bearing on the subject have appeared in this country by Lambert,[42] Smith,[43] West,[44] Gradle,[45] Stillman,[46] Fischer,[47] Diller,[48] Collins,[49] Tod,[50] Spiller[51] and Stein[52], and abroad, either coincidently with or since Hasslauer's summary by Verhoogen,[53] Hasslauer,[54] Blau,[55]

37. Gowers: Diseases of the Nervous System, 1892, ii.

38. Quincke: Ueber Meningitis serosa, Samml. klin. Vortr., new series, No. 67, 1893. p. 655. Also Ueber Meningitis serosa und verwandte Zustände, Deutsch. Ztschr. f. Nervenh., 1896, pp. 149-168.

39. Boenninghaus, G.: Die Meningitis serosa acuta, eine kritische Studie, Wiesbaden, 1897.

40. Hafslauer: Ueber Meningitis serosa, Sammelreferat internationales, Centralbl. f. Ohrenh., 1906, iv, Part 8, p. 341.

41. Dana, C. L.: Med. Rec., New York, 1897, lii, 801.

42. Lambert, A.: Alcoholism, Osler's Modern Medicine, I, 157; Bellevue Hosp. Med. and Surg. Rep., 1904, I, 113.

43. Smith, E. T.: Meningitis Serosa, Tr. Am. Otol. Soc., New Bedford, Mass., 1907, x, 550.

44. West, J. P.: Serous or Posterior Basic Meningitis: Its Early Recognition and Treatment, Ohio State Med. Jour., 1909, v, 323.

45. Gradle, H.: A Case of Serous Meningitis, Jour. Nerv. and Ment. Dis., 1906, xxxiii, 126.

46. Stillman, C. K.: Postdelirious Alcoholic Stupor, Alcoholic Cerebral Edema, (Wet-Brain), New York Med. Jour., 1908, lxxxvii, 154.

47. Fischer, J. S.: Serous Meningitis, Maryland Med. Jour., 1908, li, 158.

48. Diller: A Case of Serous (Alcoholic) Meningitis Simulating Brain Tumor, Jour. Nerv. and Ment. Dis., 1898, xxv, 441.

49. Collins, J.: Diseases of the Meninges, Twentieth Century Practice of Medicine, N. Y., 1897, x, 355.

50. Tod, H.: Lateral Sinus Thrombosis; Subsequent Meningitis (Meningitis Serosa); Recovery, Otol., sec. 30-32, Proc. Roy. Soc. of Med., 1907-1908, i, 30.

51. Spiller, William G.: Circumscribed Serous Spinal Meningitis, Am. Jour. Med. Sc., 1909, cxxxvii, 95.

52. Stein, R.: Serous Meningitis in Typhoid Fever and Its Treatment by Lumbar Puncture, Am. Jour. Med. Sc., 1910, cxxxix, 542.

53. Verhoogen, R.: La méningite sereuse, Jour. d. méd., Brux., 1907, xii, 111.

54. Hafslauer: Die bakteriologischen Befunde bei der eiterigen und serösen Meningitis mit besonderer Berücksichtigung die bei der Lumbalpunktion, etc., Internat. Centralbl. f. Ohrenh., Leipsic, 1906-7, i, 65.

55. Blau, A.: A Case of Serous Meningo-Encephalitis with Autopsy Report, Ztschr. f. Ohrenh., 1906, lii, 129.

Avellis,[56] Riebold,[57] Thiemich,[58] Paradis,[59] Axhausen[60] and L. Williams[61]. A notable phase in the development of this subject of serous meningitis in the last few years has been the interest and attention which it has received from otologists.

The etiology is so much in dispute and the descriptions of this process by various writers are so divergent, not only from the clinical but also from the anatomical standpoint, that it is impossible to define precisely what is meant by this term. This state of affairs makes it also impracticable to dwell on the mechanical problems involved. It is clearly out of the question to analyze the hundred or more articles which have appeared with this name for a subject.

In general, however, it may be said that an external and an internal form of serous meningitis are recognized and that these may be acute or chronic. In the acute external form the cortical pia arachnoid is described as being inflamed and infiltrated with round cells or leukocytes with serous exudation into the subarachnoid space and its prolongations. Sometimes the adjacent brain tissue is inflamed and edematous. When chronic, the pia may or may not be described as thickened. In the internal form there is transudation into the ventricles with dilatation. Quincke and others[62] have described the fluid as clear. Boenninghaus[63] believes that acute idiopathic hydrocephalus follows acute serous meningitis, while Thiemich[64] apparently considers that the "so-called acute hydrocephalus of childhood" and "ventricular serous meningitis" are identical.

Both Boenninghaus and Quincke have noted that non-inflammatory collections of fluid in the pia-arachnoid space are easy to mistake for serous meningitis. These pial effusions were discussed by Huguenin many years previously. He noted their association with certain atrophic states of the brain. I consider that knowledge of the subject has not greatly advanced since Huguenin's time.

Of late years much attention has been given to the abnormally large collections of fluid so often seen beneath the arachnoid membrane in

56. Avellis, G.: Oertliche Serosa Meningitis bei akuter Keilbeineiterung mit Spontanheilung, Verhandl. d. Ver. süd-deutsch. Laryngol., 1907, 454.

57. Riebold, G.: Ueber serosa Meningitis, Deutsch. med. Wchnschr., 1906, xxxii, 1859.

58. Thiemich, M.: Serous Meningitis in Diseases of Children, Pfaundler and Schlossman, Eng. Trans., 1908, iv, 376.

59. Paradis, A.: Ueber Meningitis serosa, B. George, Leipsic, 1906, p. 26.

60. Axhausen, G.: Zur Kenntniss der Meningitis serösa acuta, Berl. klin. Wchnschr., 1909, xlvi, 244.

61. Williams, L.: Serous Apoplexy, Med. Press and Circular, 1906, lxxxi, 499.

62. Thiemich (Serous Meningitis in Diseases of Children, p. 413) considers that the fluid of internal serous meningitis is usually clear but that there are slight changes which indicate inflammation of the chorioid plexus and ependyma.

63. Boenninghaus: Die Meningitis serosa acuta, p. 93.

64. Thiemich: Serous Meningitis, in Diseases of Children, p. 415.

subjects that have died of chronic alcoholism. It was primarily with the purpose of shedding some light on this subject that my paper was begun.

It became clear to me that post-mortem examinations of the brain alone would never throw sufficient light on the causation of these accumulations of fluid. I determined therefore to approach the subject by the following methods:

1. By means of an analysis of a series of cases, to show the frequency of association of pial edema with various diseases and to determine the influence of other factors such as age and nutrition.

2. By a consideration of the physical phenomena underlying the accumulation of fluid in the cranial cavity.

3. To determine whether there were any chemical differences in the cerebrospinal fluids in these various conditions that might indicate their etiological relation.

4. By the estimation and comparison of brain weights or volumes and cranial capacities in a series of cases.

With this brief introduction I now proceed to describe my observations.

PART I: ANALYSES OF CASES ACCORDING TO AGE, NUTRITION AND DISEASE

Pial edema is a very common condition at autopsy, for out of a total of the 665 cases which form the basis of this report, it was recorded 375 times, a percentage of 56.4.

The cases with pial edema (375) have been placed in one group, those without pial edema in another.

AGE

An examination of the appended table shows: First, a relative frequency of pial effusion in infants from 4 months to 5 years of age.[65]

Second, an entire absence of this condition between the ages of 6 and 15 years, followed by a rapid increase that culminates between the thirty-fifth and fortieth years with later a more gradual increase that reaches the maximum at from 80 to 85 years (old age).

The youngest subject with pial edema was 4 months old. When it is observed that in this series there were fully thirty-one cases of children, between birth and the fourth month, with dry pias, this initial date may not be without some significance.[66] The absence of pial edema in nine subjects between 6 and 15 is also significant.[67]

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65. Eighty-two infants were examined: of these eighteen presented pial effusion, that is 21.9 per cent. of the total number of cases.

66. The ages of the thirty-one children mentioned above were as follows: 13 hours, 20 hours, 2½ days, 13 days, 21 days, 1 month (three cases), 6 weeks (two cases), 7 weeks, 2 months (nine cases), 9 weeks, 10 weeks, 3 months (nine cases).

67. A case of marked pial edema in a boy of 15 who died of juvenile paresis was observed subsequently. In this case the brain shrinkage is readily explainable on pathological grounds.

In the examination of fourteen cadavers between the ages of 16 and 20 years, pial edema was found twice, or in 14..2 per cent.

In an examination of thirty-four cadavers between the ages of 21 and 25, 26.4 per cent. presented pial edema. Of the nine, five showed a slight degree, three a moderate degree including one case of alcoholism, and one a marked degree (a case of cerebral syphilis).

In forty-five subjects between the ages of 26 and 30 years, 51.1 per cent., or twenty-three presented pial edema: five slight, nine moderate (including two alcoholics) and nine marked cases. It is important to note that in the nine marked cases, six subjects had lesions usually accompanied by brain shrinkage.

In sixty-four cases between the ages of 31 and 35 years, forty cases showed pial edema, twenty moderate, twelve marked, and one extreme

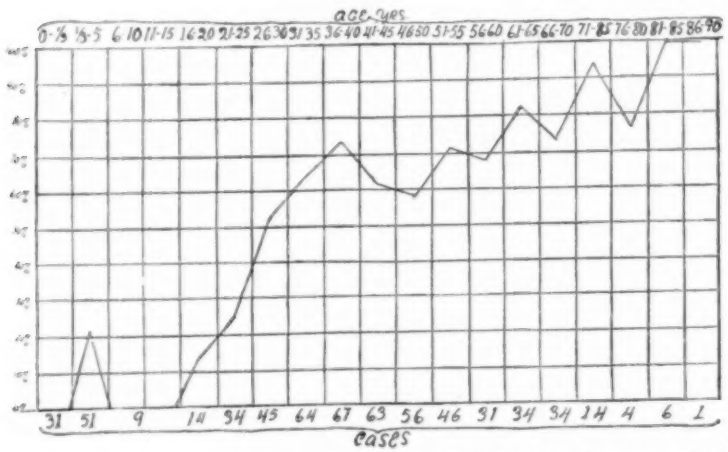

Fig. 1.—Chart, compiled from 604 cases, showing relative frequency of pial edema at various ages.

(including eight alcoholics and one case of insanity). The cause of death in the "extreme" case could not be determined.

In sixty-three subjects between the ages of 41 and 45 years, 61.9 per cent, or forty-one showed pial edema; twenty-one of moderate, eleven of marked and two of extreme grade, including in all six alcoholics.

In fifty-six subjects between the ages of 46 and 50 years, 58.9 per cent., or thirty-three, showed pial edema; twelve of moderate and eighteen of marked grade, including four alcoholics.

In forty-six subjects between the ages of 51 and 55 years, 71.7 per cent., or thirty-three, showed pial edema; thirteen moderate, seventeen marked, one extreme (pulmonary tuberculosis). This group included two cases of chronic alcoholism and one of insanity.

In thirty-one subjects between the ages of 56 and 60 years, twenty-one, or 67.7 per cent., showed pial edema; eight moderate, nine marked and one extreme.

In thirty-four cadavers between the ages of 61 and 65, 82.5 per cent., or twenty-eight, showed pial edema; nine moderate, eleven marked and three extreme cases; one case of alcoholism.

In fourteen subjects between the ages of 71 and 75 years, 92.8 per cent., or thirteen, showed pial edema; six moderately and four markedly.

The four subjects between the ages of 76 and 80 years, 75 per cent., or three, showed pial edema, all markedly. The brain of the subject without edema was normal in size and appearance.

In six subjects between 81 and 85 years of age, 100 per cent. showed pial edema; two moderately, two markedly, and two extremely.

There was one subject showing pial edema between the ages of 85 and 90 years.

NUTRITION

In neither adults or children did there appear to be any definite relation between pial edema and emaciation.

Of 357 cases of pial edema in adults, forty-nine were not fully described as regards nutrition and therefore were subtracted from the general total, leaving 308 cases for analytical purposes. The state of nutrition in these cases of pial edema was as follows:

Fat	14, or	4.5 per cent.
Fair to good nutrition	168, or	54 per cent.
Poorly nourished	34, or	11 per cent.
Emaciated	64, or	20.7 per cent.
Markedly emaciated	28, or	9 per cent.

From the above it is seen that pial edema is associated with good nutrition in the majority of instances, (59 per cent. as against 41 per cent. for the badly nourished).

Of the eighteen infants who had pial edema, two were not fully described as regards nutrition. The remaining sixteen presented findings similar to those of the adult series given above. The nutrition in these cases was as follows:

Fat	1
Well nourished	6
Poorly nourished	1
Emaciated	6
Much emaciated	2

The question whether all poorly nourished people have pial edema is answered by referring to the data concerning the cases in my series with dry pias. In this group cachexia was present ninety-eight times unassociated with any subarachnoidal collections of fluid—a number sufficiently large to show that no relationship exists between the two conditions.

RELATIONSHIP BETWEEN PIAL AND EDEMA DISEASE PROCESSES[68]

The records were grouped according to the anatomical diagnosis with a view of determining whether any diseases or conditions were regularly associated with pial edema.

Pial edema is found on the average in practically two out of every three adults at autopsy. In our series of 542 adults, the subjects with pial edema, 355 in number, constituted 65.5 per cent. of the total number. Those without pial edema, 187 in number, comprised 34.5 per cent. of all the subjects.

It is evident that pial edema cannot be assumed to be related to any particular disease process unless it can be shown that it occurs with greater frequency with that disease than it does with other diseases. The simplest method to determine whether such an association exists for any particular disease is to compare the number of subjects which show pial edema with those which do not show pial edema. If the ratio exceed 65.5:34.5 (the ratio of our total cases as shown above), such a relationship would be indicated.

The total number of cases of a given disease from both the edema and the no-edema column was set down and the percentages computed. For example, under the heading "Adhesive Pleurisy" I found thirty-one cases associated with pial edema and twenty cases unassociated; the proportion of one to the other expressed in percentages is 64.5 and 35.5 per cent. respectively.

These figures represent the absolute percentages; since the number of cases of pial edema available for study is much larger than the number of cases without pial edema we can determine the relationship which the disease bears to the disease process in question by the use of a method which does away with the necessity of directly contrasting two unequal series. This is accomplished by reckoning percentages in each column (i. e. the pial edema, and the non-edema column) separately and then by comparing the percentages so obtained. The results in each case are found to be independent of the number of cases in either series, as they represent proportions only. Their value consists wholly in their use for purposes of comparison.

Using this method we reckon first the percentage of adhesive pleurisy (thirty-one cases) in the pial edema column (355 cases); this gives us the figure 8.7 per cent. We then similarly reckon the percentage of adhesive pleurisy (twenty cases) to the 187 cases of the "control" series which is found to be 10 per cent. These percentages being compared with one another indicate that adhesive pleurisy occurs with about the

68. The tabulated cases on which these statistics are based were so extensive that it was found impracticable to include them in this article. I shall be very glad to submit them to anyone interested.

same frequency both with and without pial edema, since the proportion of occurrence of the lesion is nearly the same in either series. If now we should find that for any given disease we had a high percentage in the pial edema column, while much lower in the no-edema column, we should infer that the lesion either played some etiological rôle or was at least definitely associated with pial edema. If on the other hand we should find the percentage in the pial edema column level with or below the percentage for the same disease in the other column we should decide that the disease bore no particular relation to pial edema.

It will be at once observed that a negative result is attained when the percentages for a given disease are the same or nearly the same in the pial edema and the control columns.

It was considered best to draw conclusions only where the figures were high enough to lend value to such percentages and for this reason lesions that appeared a few times only on the chart were not emphasized.

As a result of my preliminary studies in children and young people, it seemed wise to omit all cases under maturity from the disease columns, since it is possible that in them certain unexplained factors of development might result in confusion.

Acute Parenchymatous Nephritis.—Reckoning the percentages by the method already explained, I found that acute parenchymatous nephritis was present in 10.9 per cent. of all cases with pial edema, and in 10.6 per cent. of all the cases of the series without pial edema.

Chronic Interstitial Nephritis.—Reckoning the percentages in each column separately, chronic interstitial nephritis was found present in 32.9 per cent. of all cases with pial edema and in 30.4 per cent. of all cases without pial edema. The small granular kidney was present in 18.5 per cent. of all subjects having pial edema and 15.5 per cent. of all subjects without pial edema.

These figures do not indicate any essential relationship between pial edema and this type of kidney lesion.[69]

Taken altogether our figures indicated an absence of association between pial edema and acute or chronic Bright's disease.

Syphilis.—Aside from paresis, which will be referred to again, the figures of the table did not suggest that general syphilitic infection plays a causative rôle.

69. In forty cases with pial edema the microscopical sections showed no trace of any kidney lesion, while in about the same number of cases there were noted only slight or beginning renal changes. It should be noted that the single case of uremia which we had, showed a slight degree of pial edema. There was no moisture of the cut surface apparent to suggest cerebral edema, no flattening of the convolutions or any other sign characteristic of the brains described by Traube.

Chronic Pulmonary Tuberculosis.—This was present in 16.3 per cent. of all cases of pial edema and in 26.7 per cent. of all cases without pial edema.

Chronic Cardiovalvular Disease.—The figures obtained were 10.9 per cent. with pial edema and 11.7 per cent. without.

General Arteriosclerosis.—The figures obtained were 12.9 per cent. with pial edema and 9.4 per cent. without pial edema. These figures do not suggest a relationship between pial edema and arteriosclerosis.

Anemia.—We had only four cases of anemia. Two of these were associated with pial edema and two were not.

Advanced Alcoholism.—Here was found the first really significant evidence of relationship between pial edema and a disease process. Altogether there were eighty-nine cases of chronic alcoholism in the series. Of these seventy-two subjects had pial edema, or 80.9 per cent., while the remaining seventeen had dry pias, or 19.4 per cent. Reckoning the percentages for each column separately I found that chronic alcoholism was present in 20.2 per cent. of all our cases with pial edema and present in only 9 per cent. of all cases without pial edema. The frequency with which pial edema occurs in chronic alcoholism is thus represented by the ratio 20.2 : 9, the latter figure being taken to represent the proportion of chronic alcoholics in which no pial edema is present. It may thus be said that pial edema occurs in something like two-thirds of all cases of chronic alcoholism.

Pial Edema Associated with Transudation in Other Parts of the Body.—A. Localized or Generalized Subcutaneous Edema: My tables showed:

1. Localized edema of the subcutaneous tissues occurs apparently without special relation to pial edema.

2. Generalized edema: Anasarca showed a slight preponderance in the pial edema column, but the small number of cases quoted rendered this proportion of little or no value.

3. Ascites: The same thing may be said of ascites as of anasarca.

B. Polyserositis: I had a sufficient number of cases (forty-four) to warrant me in drawing conclusions from the percentages obtained. The percentage of serositis cases was slightly higher in the control column (20 per cent.) than in the pial edema column (18 per cent). We therefore concluded that polyserositis is not associated with pial edema regularly and that it does not have necessarily the same causative factors.

Condition Associated with Acute Toxemia.—I had 466 cases which were considered as belonging in this category; 304 of these presented pial edema; the remaining 162 were not associated with this condition.

Reckoning the percentages of each series as already explained, I found acute toxemia in some form present in 85 per cent. of all cases that had no pial edema.

Conditions Associated with Bacteriemia.—There were 191 cases that could properly be grouped under the heading of bacteriemia; 111 of these presented pial edema, the remaining eighty had no pial effusion. I thus found bacteriemia present in 31 per cent. of all our cases of pial edema, and present in 42 per cent. of cases without pial edema.

Chronic Inflammatory Lesions in the Serous Cavities.—I had altogether 104 cases that were included under this heading;[70] sixty-four of these showed pial edema, while forty were unassociated with pial edema.

Chronic inflammation of the serous cavities was thus present in 18 per cent. of the cases of pial edema and present in 21.3 per cent. of the cases without pial edema.

Chronic Gastritis.—This condition was present in 13.2 per cent. of the cases with edema of the pia and in 13.9 per cent. of the cases which did not present pial edema.

Malignant Tumors.—The figures for these cases disclose nothing of significance.

Status Lymphaticus.—Of the fifteen cases of status lymphaticus in our series, twelve brains were large enough to completely fill the skull cavity. Pial edema was present in only three.

From the considerable proportion of large or fully developed brains noted with status lymphaticus, it might be inferred that we had here to do with a brain hypertrophy similar to that indicated by Anton[71] and described by Bartel[72] in some of his "status" cases. Such an inference should not receive undue emphasis; first, because complete weight records are not available in our series, and, second, because a large proportion of our subjects happened to be young people in whom brain volume is usually considerable.

Insanity.—The psychopathic cases, most important because of the possibility of organic changes being present, were too few in number for comparative figures.

SUMMARY

Age.—Edema of the pia was not found in my series before the fourth month. It occurred with moderate frequency from the fourth month to the fifth year. Between the fifth and sixteenth years it was absent. Beginning with the sixteenth year it rapidly increased in frequency to the period between the thirty-sixth and fortieth years,[73] when, following a slight sharp decline, it continued to increase though less rapidly throughout the later periods of life, becoming universal in old age.

70: Cases of serositis not included in this summary.

71. Anton: Wahre Hypertrophie des Gehirns mit Befunden von Thymusdrüsen und Nebennieren, Wien. klin. Wchnschr., 1902, xv, 132.

72. Bartel, Julius: Ueber die hypoplastische Konstitution und ihre Bedeutung, Wien. klin. Wchnschr., 1908, xxi, 783.

73. A time of life in which there is a very high death-rate among alcoholics.

Nutrition.—Pial edema occurs independently of changes in the nutrition of the body.

Disease Conditions.—1. Pial edema does not appear to bear any particular relationship to the following common conditions: chronic nephritis; chronic pulmonary tuberculosis; chronic cardiovalvular disease; acute toxemia; bacteriemia; chronic inflammatory lesions in the serous cavities, and chronic gastritis.

2. Pial edema is definitely associated with chronic alcoholism, occurring in more than two-thirds of all cases.

3. There were too few cases of syphilis, anemia and insanity to permit me to form conclusions in regard to these cases.

In conclusion I wish to emphasize, first, the progressive increase of pial edema after puberty; second, the absence of any relationship between pial edema and nutritional changes in the body at large; third, the negative findings as to association between pial edema and the general disease processes studied, except alcoholism.

PART 2. THE MECHANICS AND CHEMISTRY OF THE SPINAL FLUID AND THE ANATOMY AND PHYSIOLOGY OF THE MEMBRANES

Having determined the relationship which pial edema bears to most of the important diseases, we are now in a position to study the character of the fluid present in this condition.

NORMAL DISTRIBUTION OF CEREBROSPINAL FLUID

The cerebrospinal fluid is present within the confines of the subarachnoid space, the ventricles of the brain, the perivascular spaces and the central canal of the spinal cord. It is limited externally by the arachnoid membrane (external to which, over the cortex, lies the subdural space) and internally by the pia.

DISTRIBUTION OF THE FLUID IN PIAL EDEMA

In pial edema we find that the distribution of the fluid is the same as above stated, but that it is greatly increased in amount. The peculiarities as regards localization are as follows:

1. It is constantly found on the superior surface of the cerebral hemispheres, especially over the vertex.

2. It is found on the superior surfaces of the frontal lobes in relatively less amount.

3. The anterior and posterior cisternæ are distended.

4. It is found often as bleb-like accumulations on the posterior and inner margins and on the superior surfaces of the cerebellar hemispheres.

5. There is occasionally a similar accumulation on the anterior poles of the temporosphenoidal lobes.

6. There is occasionally an apparent increase of fluid in the perivascular spaces.

7. There is occasionally considerable moisture of the brain tissue.

8. There is occasionally increase of fluid in the subarachnoid space of the cord.

9. Usually there is an increase of fluid in the lateral ventricles.

10. It is rare to see any increase over the lateral regions of the cerebral cortex.

No increase of fluid has ever been observed by me in the following places:

A. The under surface of the frontal lobes.

B. The under surface of the temporosphenoidal lobes.

C. The inner surface of the cerebral hemispheres.

We thus observe a general tendency on the part of the excess fluid to occupy a position above that of the brain tissue proper.

THE APPARENT SIGNIFICANCE OF THIS DISTRIBUTION

The localization of the fluid as given above is in marked contrast to that of the exudate in most cases of suppurative meningitis, especially in the epidemic type. As is well known, in most cases of meningitis the exudate is found chiefly at the base—a phenomenon that is especially noticeable in tuberculous and epidemic meningitis. The experience of this laboratory is fully in accord with the above statement and points to a tendency on the part of inflammatory changes in the meninges either to begin at the base and spread thence over the cortex, or to remain localized at the base.[74]

The above localization of the fluid of pial edema is in itself suggestive of the action of gravity—and it is the one which the fluid would take were there any additional room within the cranial cavity, for the reason that as the specific gravity of the brain (1.038) is greater than that of the fluid in which it lies (1.002-1.010), the brain then would naturally seek a dependent position, forcing the fluid to a higher level.

The presence of the fluid in the cisternæ pontis (ant. subarachnoidean space) has already been mentioned.

In performing an autopsy, however, some care is necessary in order to see the fluid *in situ;* for although the arachnoid at these points is normally somewhat thicker, it is at the same time unsupported and thus is readily torn when the brain is lifted up, allowing its contents to drain away into the cranium.

When the anterior subarachnoid space is ruptured, the fluid from the posterior immediately drains across the crurae cerebelli and thence into the skull cavity.

74. For a consideration of this subject dealing with meningitis, I would refer the reader to the recent article by W. J. Elser and F. M. Hunton: Studies in Meningitis, Jour. Med. Research, 1909, xx. 371.

To what degree evacuation of the lateral ventricles follows this draining through rupture of the cisternæ is difficult to say, but that it is relatively slow there is every reason to believe.

The evacuation of the fluid over the cortex after removal of the brain also takes place gradually, apparently because the septa of the subarachnoidean chambers offer a partial obstruction to the flow of the fluid. In some cases the arachnoid reveals an almost gelatinous mass but possibly this may be due to clotting of the fluid after removal.

That the fluid over the cortex is enmeshed is shown by the following facts:

1. The fluid over the cortex may remain *in situ* some time after the brain is removed.

2. Puncturing the dependent areas over the cortex sometimes results in the evacuation of only a small area about the site of the puncture. To illustrate this fact we may cite the following:

CASE 1879.—Pia arachnoid moderately distended with clear slightly yellowish fluid, most marked over the convexity. A small puncture (about 5 mm. in diameter) was made over one of the sulci, the probe passed down through some watery and slightly gelatinous tissue to the cortex. The fluid about this puncture drained away leaving a depressed area 1 cm. in diameter, but the fluid beyond this area was apparently unaffected at the end of an hour.

The best way to maintain the cisternæ intact, according to my experience, has been to insert the calvarium hook beneath the occipital protuberance and tear off the calvarium from below upward, instead of from above downward (the usual practice). The dura being then cut away, the frontal lobes can be lifted up disclosing the cisternæ unruptured.

The pathologist has usually considered that an excessive amount of fluid at the base and the distention of the cisternæ was an indication of an increased or high intracranial tension during life. Although it may be granted that this is the explanation for a large number of cases, we must not forget that it is not conclusive evidence. The fallacy of conclusions based on such evidence is well illustrated by the conclusion drawn by the ancient Greeks on post-mortem evidence alone that the aorta contained blood mixed with air.

THICKENINGS OF THE ARACHNOID

In a considerable number of all pial edema cases there is a greater or less degree of opacity and thickening of the meninges. Sometimes this is chiefly limited to the area over the superior surface of the cortex along the longitudinal sinus; again it is found over cortex and cerebellum, and occasionally it has an even more generalized distribution.

In every case examined by me this opacity was found to be due to connective tissue thickening of the arachnoid, involving slightly the pia-arachnoid trabeculæ, the pia itself showing no change.

This lesion consists of a proliferation of the fixed connective tissue elements without exudation or vascular changes.

That a process of this essentially proliferative character arising at a distance from the blood-vessels[75] should be the cause of the large fluid accumulations seems hardly possible.

CHEMISTRY OF FLUID IN PIAL EDEMA

The final determination as to the inflammatory or non-inflammatory character of the fluid rests in the last analysis with the chemical examination. It is a well-known fact that fluid collected after death is worthless for examination, since post-mortem changes render chemical tests of doubtful value.[76] The most satisfactory method is to collect the fluids intra vitam and to verify the findings thus obtained at autopsies. Such procedure, naturally, is attended with many disappointments.

With the exception of one case reported by Dufour,[77] I have so far been unable to find in the literature any satisfactory record of analyses of spinal fluid from subjects of "wet-brain." A specific test for serum albumin or globulin rather than for protein should be of value in determining the question of possible inflammatory influences. Serum albumin is not a normal constituent of cerebrospinal fluid[78] and therefore its presence in the class of cases under discussion should indicate an exudative or transudative process. The absence of traces of serum albumin, in the light of our present knowledge of the secretory origin of the cerebrospinal fluid, would therefore indicate that the spinal fluid is the product of normal secretion. Professor Hastings has kindly supplied me with a series of analyses on this class of cases, and these will now be considered.[79]

A spinal fluid from a subject of alcoholic "wet-brain" examined by him showed a protein content of 0.005 per cent., a minimum normal figure.

The figure for protein quoted above speaks strongly against the presence of either transudate or exudate in the spinal fluid of these cases. Professor Hastings analyzed several other specimens of alcoholic "wet-brain" without reference to the protein content.

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75. The blood-vessels lie close to the pia.

76. Myers, V. C.: The Cerebrospinal Fluid in Certain Forms of Insanity with Special Reference to the Content of Potassium, Jour. Biol. Chem., 1909, vi, 115.

77. Dufour, H.: Cytologie du liquide céphalo-rachidien dans un cas de méningite chronique alcoolique, Bull. et mém. Soc. méd. d. hôp. de Paris, 1901, xviii, 1035.

78. Halliburton in Kirke's Physiology, Ed. 1908, p. 178.

79. Spinal Fluid Analyses in Alcoholic Wet Brain Cases, loaned by Professor Hastings of Cornell University.

The amounts in these cases ranged from 25 to 88 c.c.; all specimens were clear, sterile and free from coagulum or sediment. The cytological count was as given in Table 1.

TABLE 1.—CELL-COUNT—100 FIELDS

Case	Polys.	Small Monos.	Endothelial Cells	N. B. Cs.
1	0	2	0	12
2	0	7	1	18
3	0	6	0	27
4	0	1	2	1,456 *
5	0	1	0	0
6	0	3	0	0
7	0	1	0	1
8	0	0	0	0

* First tube contaminated with blood.

The conclusions from these analyses were that the fluid of alcoholic "wet-brain" did not differ from normal cerebrospinal fluid.

CIRCULATORY CHANGES IN THE MEMBRANES WITH PIAL EDEMA

It is well known that it is difficult to determine from post-mortem findings the circulatory conditions which were present during life in cases of pial edema, since alterations in the vascular system of the brain occur frequently just prior to and at the time of death.

My findings in regard to the condition of the meningeal circulation in pial edema (from post-mortem study of 100 cases) are as follows:

	No. of Cases
1. Active congestion of membranes, brain normal	12
2. Passive congestion of membranes, brain normal	21
3. Active and passive congestion of membranes, occurring together, brain normal	12
4. Active congestion of membranes with anemia of brain	1
5. Passive congestion of membranes, with anemia of brain	1
6. Active congestion of membranes and brain	5
7. Passive congestion of membranes and brain	7
8. Active and passive congestion of membranes and brain	10
9. Membranes and brain normal	20
10. Pia-arachnoid normal, brain anemic	4
11. Pia-arachnoid normal, brain congested	1
12. Anemia of brain and membranes	6

The commonest condition found was thus passive congestion of the membranes (present in 21 per cent.). The next most common was an apparently normal condition of the vessels of the brain and meninges (20 per cent.). Active congestion of the membranes and a condition of active and passive congestion of the membranes, occurred in 12 per cent. Anemia of the membranes and brain was present in 6 per cent. Altogether passive congestion of the membranes (either alone or combined) occurred in fifty-one cases (51 per cent.), whereas active congestion was

present in only forty cases (40 per cent.). The preponderance of passive congestions in this series agrees with the statement of Kaufmann[80] that most of the cerebral congestions observed at autopsy are of the passive type.

The frequent occurrence of passive congestion can hardly be taken as an indication that passive congestion has any special influence in the production of pial edema because there is nothing to show that it is more common with pial edema than with the general run of autopsy cases. Furthermore, the wide variety of other vascular conditions cited in this series shows that pial edema bears no constant relation to any particular circulatory condition as seen at autopsy.

PART 3. THE PHYSICS AND MECHANICS OF PIAL EDEMA

My observations thus far have been with a view to determine under what conditions pial edema is found. Let us now consider from a more theoretical standpoint the mechanics involved in the causation of accumulations of fluid in the pia-arachnoid. Two hypotheses present themselves:

1. The accumulation of fluid is the result of an increase of secretory activity of the chorioid plexus, or a lack of resorption, leading to a compression of the brain substance, or

2. The fluid has simply collected as a result of some undetermined process leading to a reduction in size of the brain.

The first hypothesis to be discussed is whether the fluid can actually compress the brain so as to give rise to the appearances met with in pial edema.

Before doing so, however, we must review certain well-established mechanical principles, a correct understanding of which is essential to a comprehension of some of the more complex problems in connection with pial or cerebral edema and serous meningitis.

It will not be necessary to sketch the outlines of the study of intracranial mechanics since the time of the second Monro.[81] Let me present only the points that are involved and endeavor briefly to show their bearing on our subject.

Of fundamental importance is the old question "Is the craniospinal canal independent of the influence of atmospheric pressure?"

Certain early writers, as Monro, Kellie,[82] Abercrombie and Reid,[83] and nearly all modern writers, among whom may be included Naunyn

80. Kaufmann, Eduard: Lehrbuch der speziellen pathologischen Anatomie, Berlin, 1904, p. 983.

81. Monro, Alexander: Observations on the Structure and Functions of the Nervous System, Edinburgh, 1783.

82. Kellie, George: Reflections on the Pathology of the Brain. Tr. Med.-Chir. Soc. Edinburgh, 1824, i, 84.

83. Reid: Physiol., Anat. and Path. Researches, xxv.

and Schrieber,[84] Falkenheim and Naunyn,[85] Horsley and Spencer,[86] Horsley,[87] Spencer,[88] Roy and Sherrington,[89] Hill,[90] Kocher,[91] Cushing[92] and many others, have decided that it is.

The earlier negative conclusions of Burrows[93] and Donders[94] were seriously considered for over half a century after their promulgation.[95]

Leonard Hill's argument in favor of the absence of atmospheric pressure within the skull cavity was as follows:

> If the spinal cord of a dog be divided or the splanchnic nerves be cut and the animal be placed in the vertical feet-down position, the blood-pressure in the brain will under the influence of gravity, fall to zero. If the skull be now trephined, and the dura be rapidly opened, the brain, which was before in close apposition with the dura, may now be seen collapsing under one's very eyes, as it is emptied of blood by atmospheric pressure.[96]

Additional evidence in confirmation of Leonard Hill's view that atmospheric pressure was absent in the skull cavity was obtained by the following experiments:

> EXPERIMENT 1.—A trocar was introduced into the spinal canal of a prone intact cadaver and a small amount of fluid ran out owing to persistence of the pressure existing during life. No more escaping, suction was applied by means of a syringe and a little more fluid was obtained (altogether about 3 c.c.). The trocar was then removed and the calvarium opened. The cisternæ contained the usual amount of fluid and likewise the spinal canal.

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84. Naunyn, B., and Schrieber, J.: Ueber Gehirndruck, Arch. f. exper. Path. u. Pharmakol., 1881, xiv, 1.

85. Falkenheim, H. and Naunyn, B.: Ueber Hirndruck, Arch. f. exper. Path. u. Pharmakol., 1887, xxii, 261.

86. Horsley, V., and Spencer, W.: Phil. Tr., 1891,

87. Horsley, Sir Victor: The Mode of Death in Cerebral Compression and Its Prevention, Quart. Med. Jour. London, 1894, ii, 305; The Structure and Functions of the Brain and Spinal Cord, P. Blakiston's Son & Co., Phila., 1892.

88. Spencer, W.: The Central Nervous Mechanism of the Respiration, Arris and Gale Lectures, Lancet, London, 1895, xxxi, 532.

89. Roy, C. S., and Sherrington, C. S.: On the Regulation of the Blood Supply of the Brain, Jour. Physiol., 1890, xi, 85.

90. Hill, Leonard: The Physiology and Pathology of the Cerebral Circulation, London, 1896, Churchill.

91. Kocher, T.: Hirnerschütterung, etc. Specielle Pathologie und Therapie in Nothnagel, Wien, 1901, Ed. 2, Part, 3, ix.

92. Cushing, H.: Some Experimental Clinical Observations Concerning States of Increased Intracranial Tension (Mutter Lecture), Am. Jour. Med. Sc., 1902, cxxiv, 375; The Blood Pressure Reaction of Acute Cerebral Compression, etc., Am. Jour. Med. Sc., 1903, cxxv, 1017; A Discussion of Some Remote Effects of Cranial Injuries, etc., New York Med. Jour., 1907, lxxxv, 97, 61, 208.

93. Burrows, George: Disorders of the Cerebral Circulation and on the Connection Between Affections of the Brain and Diseases of the Heart, Philadelphia, 1848, Lea and Blanchard.

94. Donders, F. C.: Nederl. Lancet, 1850.

95. Reynolds and Bastian: Congestion of the Brain, in Reynolds' System of Medicine, 1879.

96. Hill, Leonard: The Physiology and Pathology of Cerebral Circulation, p. 36.

EXPERIMENT 2.—Calvarium removed first. Cisternæ intact and seen to be full of clear fluid. Spinal puncture; 12 c.c. fluid came through cannula as if under slight pressure. Cisternæ re-examined and found full as before. Brain covered with wet cloths; in ten minutes fluid at the base had all disappeared into the cord.

The first experiment shows that outside air-pressure does not influence the contents of the craniospinal canal, since it was impossible to evacuate the fluid (except that in excess, and a slight amount in addition, due, possibly, to the stretching inward of the spinal membranes) through the single opening.

When, however, as in Experiment 2, a second opening was made and outside air-pressure admitted, there was no obstacle to the ready evacuation of the fluid in the direction of gravity.

The principle involved in these experiments is very easy to demonstrate with suitable apparatus. It will be observed that the fluid in the craniospinal canal in the first case has behaved as might be expected were atmospheric pressure absent.

There are certain anatomical features that require consideration in this connection.

Figure 2 represents the craniospinal canal, to all intents and purposes a closed cavity: the heavy black line its bony confines; the thinner line within represents the arachnoid which determines the outer limit of spinal fluid. While this membrane is not actually adherent to the overlying dura and bony walls, it lies in close apposition within the skull and is therefore incapable of any distention outward. In the spinal canal, however, it (together with the dura) lies like a sac at some distance from the bony walls, being separated from these walls by loose and compressible areolar tissue containing a plexus of veins.[97]

Any increase of fluid within such a cavity must find room through distention of the sac outward.[98]

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97. Schafer, E. A.: In Quain's Anatomy; Spinal Cord and Brain, Part 1, p. 3, Longmans, Green and Co., London, 1893.

98. The suggestion that the theca vertebralis plays a part during life in the accommodation of excessive amounts of spinal fluid and the production of high intracranial pressure will doubtless arouse opposition among those who have demonstrated vascular relationship to pressure phenomena. I do not, however, disagree with Dr. Ferrier's statement that under normal conditions the ebb and flow between the cranial and spinal cavities is so small as to be practically a negligible quantity, but I desire to point out that no experimental work so far done is of much value in helping us to reach conclusions in the present work: largely because of the fact that none of these experiments has been arranged so as to show what mechanical changes take place when resorption of spinal fluid is prevented and when the high pressure is caused by an excessive amount of the fluid itself. My suggestion that distention of the theca is a factor is based on a study of the behavior of fluids within the craniospinal canals of cadavers. The distensibility of the sac under these circumstances has long ago been demonstrated, but Dean (Jour. Path. and Bacteriol., 1893, i, 28) and others have been inclined to doubt whether such a process could take place in living subjects.

It is of course unlikely that such a process would take place unless there were some hindrance to resorption.

It will be readily seen that while fluid can, at the outset, be forced into this sac without greatly raising intracranial pressure, after an amount has been forced in sufficient to crowd the tissue of the surrounding space and stretch the membranes considerably, there will be an ever-increasing resistance for each cubic centimeter forced in, until finally a point is reached at which no more fluid can be introduced, owing to the surrounding tissues having reached their limit of compressibility. It is the elastic recoil of these membranes which are put on the stretch, and the adjacent tissues which are compressed that, to a certain extent, gives the measure of intracranial tension, and thus when a cannula is introduced into this distended sac the tension of the tissues and membranes causes the expulsion of excess of all fluid, until the pressure is relieved.

Not all of the fluid, however, drains away, for a certain amount is necessary to fill various areas in and about the brain substance and the spinal cord. In the skull cavity the amount of this fluid scarcely varies

Fig. 2.—Diagram of craniospinal canal; heavy black line, bony confines; thinner line within, the arachnoid which determines the outer limit of spinal fluid.

since it cannot increase against the bony walls, nor can it diminish in amount anywhere without producing a vacuum at that point.

In the canal, on the other hand, the sac will retain only sufficient fluid to maintain equilibrium; that is to say, although a slight excess positive pressure is normally maintained, enough fluid will run out of a cannula to reduce this slight positive pressure to zero. Zero does not mean absence of fluid, but merely that the pressure within the spinal canal has dropped to the normal air-pressure.

Having considered the relation of atmospheric pressure to the skull cavity, and obtained some idea as to the relationship which exists between the membranes and the phenomena of intracranial tension, we may now go a step further and attempt to determine the effect of the factors just discussed on the brain itself. The difficulties involved in a study of this phase of our problem are all the greater when we realize that we know very little about two essential factors, i. e., first, the density or compres-

sibility of brain tissue and second, the permeability of the brain to fluids under pressure.

Our task now is to determine whether, according to the laws of physics and hydraulics, it would be possible for the brain (its blood-vessels excepted) to suffer compression through general increase of intracranial pressure.

The subject of compressibility must first be considered. Compression, broadly speaking, is brought about through expression of content. It is true that molecules are very slightly compressible, but, as indicated below,[99] reduction in size from molecular compression would be so insignificant as to deserve but little attention.

For example, take a dry sponge; it is readily compressed in the hand through expulsion of the air molecules from its chambers. On being allowed to soak up water it gains in size and weight but still remains compressible through the ready loss of the water under pressure. If the same saturated sponge be now placed in an air-tight rubber bag which fits snugly at all points, compression is no longer possible, since there is now no longer any means of escape for its fluid contents.

The same principle applies to all homogeneous semifluid bodies; compression takes place by expression of air or fluid content where possible but when air or fluid cannot be expressed the body is termed incompressible.

Since, then, compression sufficient to be visible can only take place through expression of content, it is only fair to inquire whether such compression could occur within the skull cavity. An attempt to force fluid into a receptacle already filled with a solid or fluid would not result in an increase in the amount within the receptacle, but its molecules would simply transmit the added pressure to the walls and there is no reason to assume that the brain is to be looked on as an exception to this physical principle. Compression cannot take place without corresponding allowance being made for the displaced substance in the enclosing medium. Lacking this allowance any reduction of size is impossible.

A converse process, i. e., brain swelling, requires a corresponding displacement of content that is under ordinary circumstances allowed for by the evacuation of spinal fluid—a process that takes place when tension is somewhat raised.

While there is, according to the above explanation, no ground for the belief that general high intracranial pressure could bring about visible changes in the size or contour of the brain, it is barely possible that pressure may be a factor in inducing molecular compression, for although such molecular compression as might result from those degrees of intra-

99. Water, which is relatively incompressible, has increased in weight only about 0.03 pound to the cubic foot at a depth of 350 feet. Treatise on Hydraulics, Merriman, 1906, p. 11.

cranial pressure that have been registered clinically are very slight when judged from the standpoint of the physicist, still so sensitive a tissue as the nerve cell is known to be, might appreciate the very small increases of molecular densities brought about in this manner.

We are not, however, justified in speculating on the chances of molecular compression within the brain until more is known about the compressibility of gray matter; if, for instance, this is slight, pressure would be transmitted through the brain to the surrounding bony confines, the intervening cells of the gray matter being but little affected. On the other hand, were the compressibility greater, pressure would not be so readily transmitted and a slight amount of molecular compression would doubtless result.

The influence of pressure from general causes has already been pointed out; we may now briefly contrast with these the effects of pressure due to local conditions, namely, those caused by hemorrhage or due to tumor growth.

The multiplication of tumor cells exerts, as in other organs, its first effect locally—namely, in compression and pressure-atrophy of the adjacent tissues and in compression of the adjacent vascular structures in the brain. Further compensation for any increase in growth or hemorrhage develops at the expense of the spinal fluid, which is resorbed, while when intracranial tension exceeds that in the venous structures the latter become somewhat compressed.[100]

Striking post-mortem evidence of compression through any intracranial growth is seen in the marked flattening of one or both hemispheres, the dry pia and the marked diminution in amount of blood found in the pial vessels.

For these reasons I believe that compression of the brain by the fluid in cases showing pial edema is an impossibility, and that the appearances observed in cases of pial edema are not attributable to the pressure of the fluid. These appearances are thus the result of some other agency, in all probability they represent a redistribution or replacement process.

PART 4.—PHYSICS AND MECHANICS OF PIAL EDEMA

For the purpose of determining whether or not I had to deal with a replacement process, I began the rather elaborate system of post-mortem observations which are now to be described.

The cases on which these observations were made were taken from the general autopsy service of Bellevue Hospital. The technic was as follows:

100. The subject of the effects of pressure on the vascular structures within the skull has received so much attention of late that elaboration in this paper would seem superfluous. The following contributions are especially important: Ferrier, David: The Harveian Oration on the Heart and Nervous System, Lancet, London, 1902, ii, 1099; Cushing, H.: ibid.

TECHNIC

When possible the calvarium was removed before the thorax was opened in order to prevent a redistribution of the blood. Many times, however, it was impracticable to halt the general autopsy work for this rather considerable interval and the result was that when the thorax was opened and the large veins were cut, as soon as the calvarium was opened and the relative negative pressure within the skull cavity removed, a considerable amount of blood would drain into the thorax from the vessels of the head.

The chief effect of this loss of blood was a reduction in the volume of the brain, causing a discrepancy between the volume of the cranial cavity as afterward registered and the total measured cranial content. The influence of this factor on the weight, specific gravity and volume of the brain, however, need not be considered, as when the blood was not evacuated into the thorax, it would be lost as the brain was being removed, and thus would not enter into subsequent computations.

As soon as the calvarium was removed, a pan was placed beneath to catch the drippings, and the tentorium carefully cut away and laid aside. The hemispheres were gently pushed apart along the great longitudinal furrow, and a small incision made through the corpus callosum into each lateral ventricle, the contents of which were withdrawn by a pipette and measured.

The brain was then removed and allowed to drip into a pan until the watery fluid over the cortex and elsewhere, had quite disappeared. It was then weighed in the air and its weight recorded. Following this it was weighed in water at 15 C. with the same balance and its specific gravity computed.

It is important to note here that considerable variation in specific gravity was unavoidable owing to the fact that in many of the brains it was impossible to get rid of all the spinal fluid which was retained in pockets and corners of the sulci. This increased the weight in air, but not in water, and as a very few grams weight will make quite a wide variation in specific gravity, it will be seen that I was here often confronted with an important source of error.

The brain proper having been disposed of, the drippings, the free fluid in the calvarium, and the ventricular fluid, were carefully collected and measured.

The portions of dura cut away were measured in water giving the number of cubic centimeters displaced, and, finally, the capacity of the skull cavity was measured by means of dried peas.

By the addition of the total fluid content of the calvarium with the dura and the brain volume (in c.c.), a fairly accurate estimate of the total cranial content is arrived at. Comparing this figure with that representing the cranial volume a very slight error is observed in those cases in which the cerebral blood was allowed to escape into the thorax previous to the examination of the head. In the latter cases the discrepancy represents this loss and can be readily identified by a study of the chart.

Having ascertained the above data, it was thought to be best for purpose of study to arrange the cases in groups corresponding to the amount of pial edema present.

On examining Table 2, in reference to the specific gravities, the recognized tendency for brains to become lighter at the extremes of age is observed.

There is, however, a most important point which these tables have clearly brought out; i. e., that there is a gradually increasing discrepancy between the capacity of the brain cavity and the volume of the brain, which is directly proportional to the degree of pial edema present.

In Group 1, cases without pial edema, we see that the average discrepancy is only about 29 c.c., this figure being presumably the equivalent

TABLE 2.—CASES ARRANGED IN GROUPS ACCORDING TO AMOUNT OF EDEMA PRESENT

GROUP 1.—CASES HAVING NO EDEMA

Acc. No.	Age.	Anatomical Diagnosis.	Amount of Fluid in Ventricles (c.c.).	Specific Gravity of Cerebrospinal Fluid.	Weight of Brain (gm.).	Specific Gravity of Brain.	Volume of Brain (c.c.).	Volume (c.c.) of Excised Dura (Tentorium and Falx).	Total Fluid in Cranium (c.c.).	Total Capacity of Cranium (c.c.).	Discrepancy Between Volume of Brain with Membrane and Capacity of Skull (c.c.).
1,974	35 yrs	Polyserositis	2	Contam.	1278	1.035	1234	30	26 c.c.	1290	26
2,099	5 mos.	Fatty liver; encephalon siccum	0	Contam	576	1.033	558	0	30 m.	565	7
2,105	44 yrs.	Status lymphaticus	3	1.008	1322	1.039	1272	28	20 c.c.	1345	53
2,146	46 yrs.	Carcinoma of stomach	2	Contam.	1000	1.046	954	18	30 c.c.	1000	28

Average age (infants excluded), 39.5 years. Average specific gravity of brains, 1.0363.
Average discrepancy, 28.8 c.c. This figure represents about the normal quantity of spinal fluid found in the skull with the brain at its maximum stage of development.

GROUP 2.—CASES WITH SLIGHT EDEMA

1,959	43	Delirium tremens; chronic alcoholism	2	Contam.	1275	1.044	1218	20	30	1280	32
2,107	21	Chronic pulmonary tuberculosis	3	Contam.	1410	1.036	1362	30	50	1445	53
2,130	42	Chronic pulmonary tuberculosis	27 Clear	1.008	1275	1.039	1227	20	57	1330	83

Average age, 35.3 years. Average specific gravity of brains, 1.0397. Average discrepancy, 53 c.c.

GROUP 3.—CASES WITH MODERATE EDEMA

Acc. No.	Age (years).	Anatomical Diagnosis.	Amount of Fluid in Ventricles (c.c.).	Specific Gravity of Cerebrospinal Fluid.	Weight of Brain (gm.).	Specific Gravity of Brain.	Volume of Brain (c.c.).	Volume (c.c.) of Excised Dura (Tentorium and Falx).	Total Fluid in Cranium (c.c.).	Total Capacity of Cranium (c.c.).	Discrepancy Between Volume of Brain with Membrane and Capacity of Skull (c.c.).
1,963	50	Cardionephritic	6	1.007	1401	1.039	1359	29	65	1560	72
2,057	37	Brain tumor	Clear 8	Contam.	1230	1.038	1184	22	53	1270	64
2,082	33	General miliary tuberculosis	Clear 12	1.007	1271	1.035	1227	50	106	1385	108
2,101	?	Chronic pulmonary tuberculosis	Clear 5	1.003	1044	1.040	1003	21	76	1100	76
2,106	21	Chronic tuberculous peritonitis	Clear 5	1.006	1115	1.038	1074	20	58	1225	131
2,113	40	Chronic alcoholism; gangrenous cervicitis	Clear 8	1.005	1268	1.038	1221	32	90	1380	127
		Average age, 36.2 years.	Clear	Average specific gravity of brains, 1.0365.			Average discrepancy, 96.3 c.c.				

GROUP 4.—CASES WITH MARKED EDEMA

1,964	54	Carcinoma of esophagus; bronchopneumonia	4	1.009	1347	1.037	1299	35	67	1510	176
2,039	56	Acute general miliary tb.; tb. of meninges	18	Contam.	1447	1.033	1400	29	100	1635	206
2,085	1	Marasmus; congenital diplegia	.....	.....	668	1.030	646	10	Collected 100; remainder lost.	830	162
2,108	40	Chronic pulmonary tuberculosis	3	1.007	1194	1.038	1149	22	115	1340	169
2,131	67	General arteriosclerosis	24	1.007	1197	1.039	1151	30	125	1345	164
2,147	70	Chronic miliary pulmonary tuberculosis	Clear 18	.....	1335	1.038	1286	40	138	1550	224
		Average age (children excluded), 57.6 years.		Average specific gravity of brains, 1.0358.			Average discrepancy, 183.5 c.c.				

GROUP 5.—CASES WITH EXTREME EDEMA

2,052	66	Chronic interstitial nephritis	7	Contam.	1060	1.027	974	27	122	1190	189
2,148	61	Chronic tuberculous bronchopneumonia	Clear 25	.....	1231	1.041	1182	20	175	1450	228
		Average age, 63.5 years.	Clear	Average specific gravity of brains, 1.034.			Average discrepancy, 208.5 c.c.				

of the cerebrospinal fluid present. In these cases the brain may be assumed to fill the skull cavity within physiological limits.

In Group 2, where the edema is slight, there is an average total discrepancy of 53 c.c., an increase of 24 c.c. over the preceding class.

As the edema increases, there is a corresponding increase in the discrepancy. In the remaining groups it is, with moderate edema, 96 c.c.; with marked edema, 183 c.c.; and lastly, in the two cases of excessive edema in the series the discrepancy culminates with 208 c.c. as a maximum, this in spite of the fact that one of the cases examined had a very small skull. This discrepancy can, of course, be interpreted in only one way, i. e., that the brain has become so reduced in size as not to fill completely the cranial vault.

Were compression the cause of this reduction in size there should be a corresponding increase in the specific gravity of these brains, proportional to the degree of edema. This, we see, is not present; indeed, if it is permissible to say anything at all in this connection, it is that the specific gravity has fallen slightly with the higher grades of edema. To say merely that the condition is a hydrops *ex vacuo* does not, by any means, dispose of the whole subject; let us therefore resume the consideration of the data before us.

Leaving out of account the two cases cited, in very young children, we observe that the more vigorous periods of life coincide with the milder degrees of discrepancy between brain and skull cavity, while the more marked differences are exhibited in the more advanced periods of life. It has been universally recognized that shrinkage of the brain is an accompaniment of extreme old age, but the extent to which this phenomenon reaches back into the years of vigorous manhood has not been generally considered.

Table 3 shows the brain weight at different ages; for children only, by Parrot,[101] Pfister,[102] and Marchand;[103] through childhood up to the twenty-fifth year by Vierordt;[104] at all ages Boyd,[105] Meynert[106] and Handmann;[107] and from the twentieth to the ninety-fifth year, Bischoff.[108]

101. Parrot: Bull. Soc. d'Anthropol. de Paris, 1887, le Mars.

102. Pfister, H.: Ueber das Gewicht des Gehirns und einzelner Hirntheile beim Säugling und älteren Kinde, Neurol. Centralbl., 1903, xxii, 562.

103. Marchand: Ueber das Hirngewicht des Menschen, Abhandl. d. math.-phys. Classe d. kgl. Sächsischen Gesellsch. d. Wissensch., 1892, xxvii, 437.

104. Vierordt, H.: Anat. Physiol. u. Physikal. Daten und Tabellen, 1906, Jena.

105. Boyd: Phil. Tr. Roy. Soc. London, 1861, cli, 242.

106. Meynert, Th.: Das Gesammtgewicht und die Theilgewichte des Gehirnes in ihren Beziehungen zum Geschlechte, dem Lebensalter und dem irrsin, untersucht nach einer neuen Wägungsmethode an den Gehirnen der in der Wiener Irrenanstalt im Jahre 1866 Verstorbenen, Vrtljschr. f. Psychiat., 1867, ii, 125.

107. Handmann, Ernst: Ueber das Hirngewicht des Menschen, etc., Arch. f. Anat. u. Entwcklngsgesch., 1906, p. 1.

108. Von Bischoff, T. L. W.: Das Hirngewicht des Menschen (von P. Neusser) Bonn, 1880.

TABLE 3.—GROUP 1.—BRAIN WEIGHTS OF CHILDREN AND YOUNG ADULTS*

VIERORDT			PARROT			PFISTER			MARCHAND		
Age	Weight (gm.) Males	Females	Age	Weight (gm.) Males	Females	Age	Weight (gm.) Males	Females	Age	Weight (gm.) Males	Females
Newborn..	381	384	.....	.....	.....	.....	340•	330•	.....	371	361
1 month..	463	402	.....	364	331	2-4 wks..	431	396	.....	411	375
2-3 mos...	548	527	.....	490	412	2 mos...	461	415	.....	474	450
4-6 mos...	632	575	.....	575	552	3 mos...	519	504	.....	612	587
7-9 mos...	733	771	7-11 mos.	778	719	4-5 mos..	583	562	.....	.....	.....
10-11 mos.	....	693	.....	.....	.....	6-8 mos..	733	666	7-11 mos.	796	802
1 year....	944	872	.....	.....	.....	9-10 mos.	786	684	.....	.....	.....
2 years...	1,025	960	1-2 years.	964	913	11-12 mos.	851	727	.....	967	893
3 years...	1,112	1,040	.....	.....	.....	.....	958	901	1-2 years.	1,011	896
4 years...	1,327	1,138	2-4 years.	1,167	1,063	.....	1,099	1,044	2-3 years.	1,080	1,099
5 years...	1,282	1,220	.....	.....	.....	.....	1,183	1,091	3-4 years.	1,310	1,024
6 years...	1,353	1,258	4-6 years.	1,261	1,137	.....	.....	.....	4-5 years.	1,273	1,183
7 years...	1,348	1,295	.....	.....	.....	.....	.....	.....	5-6 years.	1,343	1,245
8 years...	1,366	1,150	.....	.....	.....	5-8 years.	1,219	... .			(at 5 yrs.)
9 years...	1,425	1,242	.....	.....	.....	.....	.....	.....	.....	.....	.....
10 years..	1,417	1,267	.....	.....	.....	.....	.....	.....	6-9 years.	1,360	1,242
11 years..	1,379	1,238	.....	.....	.....	9-12 yrs.	1,285	1,265	.....	.....	.....
12 years..	1,415	1,245	.....	.....	.....	.....	1,289	.....	10-14 yrs.	1,346	1,221
13 years..	1,475	1,255	.....	.....	.....	.....	.....	.....	.....	.....	.....
14 years..	1,289	1,345	.....	.....	.....	.....	.....	.....	.....	.....	.....
15 years..	1,471	1,235	.....	.....	.....	.....	.....	.....	.....	.....	.....
16 years..	1,435	1,272	.....	.....	.....	.....	.....	.....	.....	.....	.....
17 years..	1,409	1,236	.....	.....	.....	.....	.....	.....	15-19 yrs.	1,404	1,309
18 years..	1,441	1,324	.....	.....	.....	.....	.....	.....	.....	.....	.....
19 years..	1,384	1,234	.....	.....	.....	.....	.....	.....	.....	.....	.....
20 years..	1,444	1,228	.....	.....	.....	.....	.....	.....	.....	.....	.....
21 years..	1,425	1,319	.....	.....	.....	.....	.....	.....	.....	.....	.....
22 years..	1,348	1,280	.....	.....	.....	.....	.....	.....	.....	.....	.....
23 years..	1,402	1,277	.....	.....	.....	.....	.....	.....	.....	.....	.....
24 years..	1,419	1,248	.....	.....	.....	.....	.....	.....	.....	.....	.....
25 years..	1,428	1,230	.....	.....	.....	.....	.....	.....	.....	.....	.....

• Parrot's, Pfister's and Marchand's ages same as in Vierordt's column unless otherwise indicated.

GROUP 2.—BRAIN WEIGHTS AT ALL AGES*

HANDMANN			MEYNERT			BOYD			BISCHOFF		
Age	Weight (gm.) Males	Females	Age	Weight (gm.) Males	Females	Age	Weight (gm.) Males	Females	Age	Weight (gm.) Males	Females
.....	239†	247¶	.....	.....	.....	Newborn.	393	347	.....	.....	.....
7 days...	404‡	377‖	.....	.....	.....	.....	.....	.....	.....	.....	.....
8-30 days	357	357	.....	.....	.....	1-3 mos..	493	495	.....	.....	.....
.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
2-3 mos..	485	486	.....	.....	.....	.....	603	560	.....	.....	.....
4-6 mos..	650	490	.....	.....	.....	7-11 mos.	777	709	.....	.....	.....
7-12 mos.	830	817	.....	.....	.....	1-2 years.	941	845	.....	.....	.....
2 years..	1,075	998	.....	.....	.....	.....	.....	.....	.....	.....	.....
3 years..	1,208	1,088	.....	.....	.....	2-4 years.	1,097	997	.....	.....	.....
4 years..	1,185	1,173	1-19 yrs..	1,114	.....	.....	.....	.....	.....	.....	.....
5 years..	1,245	1,225	.....	.....	.....	4-6 years.	1,140	1,137	.....	.....	.....
6 years..	1,215	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
7-9 years.	1,345	1,283	.....	.....	.....	6-14 yrs..	1,304	1,156	.....	.....	.....
10-14 yrs.	1,400	1,215	.....	.....	.....	.....	.....	.....	.....	.....	.....
15-17 yrs.	1,429	1,281	.....	.....	.....	15-19 yrs.	1,376	1,246	.....	.....	.....
18-19 yrs.	1,328	1,226	.....	.....	.....	.....	.....	.....	.....	1,396	1,234
20-29 yrs.	1,392	1,252	.....	1,306	1,169	20-30 yrs.	1,358	1,239	.....	1,365	1,233
30-39 yrs.	1,367	1,246	.....	1,326	1,167	30-40 yrs.	1,366	1,222	.....	1,366	1,240
40-49 yrs.	1,358	1,247	.....	1,317	1,173	40-50 yrs.	1,348	1,214	.....	.....	.....
.....	.....	.....	.....	.....	.....	At 50 yrs.	1,352	1,208	.....	.....	.....
50-59 yrs.	1,357	1,227	.....	1,240	1,174	50-60 yrs.	1,345	1,225	.....	1,375	1,200
60-69 yrs.	1,326	1,208	.....	1,289	1,161	60-70 yrs.	1,315	1,210	.....	1,323	1,178
70-79 yrs.	1,282	1,175	.....	1,206	1,098	71-80 yrs.	1,290	1,170	.....	1,279	1,121
80-84 yrs.	1,250	1,126	80-89 yrs.	.....	1,148	Over 80..	1,284	1,127	80-85 yrs.	1,023	942

• Meynert's age grouping follows Handmann's and Bischoff's; is similar to Boyd's except when otherwise indicated.

† Boys under 49 cm. length of body.
‡ Boys over 50 cm. length of body.
¶ Girls under 50 cm. length of body.
‖ Girls from 50 to 55 cm. length of body.

The highest figures reached in Vierordt's column, Table 3 (1,475 gm.) occur at the age of 13 years in males. Among the females the highest weight recorded is (1,345 gm.) at the age of 14. This table, however, can scarcely be considered complete enough for our purposes.

Boyd's figures give the period of maximum weight as between 15 and 19 years, with a subsequent loss up to the age of 80 of about 90 gm.

Bischoff represents an irregular decline from 20 to 30 onward in males. His highest figure quoted in females, however, is between 40 and 50.

Handmann finds that the greatest brain weight occurs in males between the seventh and fifteenth years and that after the twenty-ninth year there is a gradual and steady decline. In females, curiously enough, his highest recorded brain weight (1,283 gm.) occurs in rather young children, seventh to ninth years. There is a slightly lower figure given for the period between the fifteenth and seventeenth years. There is, however, no rapid decline evident until middle age.

Peacock gives the maximum weight as between 25 and 30, Broca[109] at between 30 and 35, while Meynert's figures indicate that loss of weight begins even later in life.

Blakeman[110] concluded that the human prime in brain weight seems to fall before the twentieth year and that after this period there is on the whole a continuous fall. Taken altogether these data afford clear evidence that recessive changes within the brain begin often quite early in life, although it is evident from the study of even such limited data as I present that in some cases the brain maintains its maximum volume until its possessor is well advanced in years.

From these data there may be noted a strong tendency on the part of the age curve of pial edema as plotted out from my series of 375 cases to coincide with a curve plotted out in accordance with a scale of loss of brain weight for equivalent ages, that is to say, as the curve for pial edema rises, the average of brain weights will be found to fall correspondingly from point to point on the chart.

Apart from the sudden rise in the pial edema curve between 30 and 40 years, due to the inclusion of the large number of alcoholics dying within this period, the evidence is strong that pial edema coincides with the reduction of brain weight that is common after puberty, and, such being the case, I infer that it is secondary to a reduction in size of the brain and that it therefore represents a replacement process due to the brain shrinkage.

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109. Quoted from Quain's Anatomy, iii, Part 1, p. 178.

110. Blakeman, J.: A Study of the Biometric Constants of English Brain Weights and Their Relationships to External Physical Measurements, Biometrika, 1905, iv, 124.

Such a shrinkage is of course to be looked on as entirely physiological. The discrepancy between the skull and the brain is doubtless to a certain extent modified by the sensible shrinkage of the head diameters described by Blakeman[111] as occurring in general hospital cases, but this is really slight, being very roughly only about 5 mm. between the twentieth year and old age.

Pathological shrinkage of the brain, that due to contraction caused by disease, has long been recognized. Clapham[112] in 1873, Crichton-Browne,[113] 1879, and Mercier[114] in 1891 published observations on the subject of lessened brain weights in the insane drawn from large series of cases. Boyd's figures, with which Crichton-Browne agrees, are so tabulated as to be readily intelligible; they are given in Table 4.

Donaldson in considering this table[115] regards the last three on the list as those in which wasting of the brain takes place.

TABLE 4.—BRAIN WEIGHT IN THE INSANE AS GIVEN BY BOYD*

	MALES		FEMALES	
Diagnosis	No. of Cases	Encephalic Wt., gm.	No. of Cases	Encephalic Wt., gm.
Mania	108	1,393	107	1,227
Recurrent mania	30	1,383	33	1,238
Melancholia	52	1,335	68	1,261
Epilepsy	89	1,310	60	1,216
Dementia	49	1,307	61	1,188
General paralysis	122	1,304	30	1,162
Senile dementia	29	1,259	12	1226

* Crichton-Browne, Brain, 1879, i, 511; quoted from H. H. Donaldson's Growth of the Brain.

Kaufmann[116] describes general cerebral atrophy in connection with old age, prolonged illness, chronic lead poisoning, alcoholism and dementia paralytica. Our researches in connection with pial edema confirm the statements in regard to old age and alcoholism and indirectly disagree with that in regard to prolonged illness,[117] but do not cover the other conditions mentioned.

Altogether I may summarize by saying that pial edema follows atrophy of the brain; first, in the great majority of instances as a result of

111. Blakeman, J.: Biometrika, 1905, iv, 138. He found no shrinkage in the head diameters of criminals, but states that the subject has not been fully worked out for the general population.

112. Clapham, C.: The Weight of the Brain in the Insane, West Riding Asyl. Med. Rep., iii, vi.

113. Crichton-Browne, J.: The Weight of the Brain and Its Component Parts in the Insane, Brain, 1879, i, 504; ii, 42.

114. Mercier, C. A.: The Weight of the Brain in the Insane with Reference to Hemispheres, Lobes, Brain-Stem and Cerebellum, Jour. Ment. Sc., 1891, xxxvii, 207.

115. Donaldson, H. H.: Growth of the Brain, 1895, pp. 137-140.

116. Kaufmann, E.: Spezielle Pathologische Anatomie, Ed. 5, Berlin, 1909, p. 1094.

117. My figures already given under "Nutrition" in Part 1 have shown an absence of relationship between pial edema and wasting of the rest of the body.

physiological changes beginning at or soon after puberty; second, in a smaller group as the result of certain pathological conditions, notable among which are chronic alcoholism[118] and certain forms of insanity.

My earlier review and demonstration of the principles underlying intracranial pressure is justified, first, by the necessity of ruling out a hypothetical cause (namely, local compression) for the appearances noted in cases of well-marked subarachnoidal edema; secondly, by the evident need of restating these principles to those observers on serous meningitis who have apparently overlooked them, and, lastly, by the necessity of reviewing the fundamentals before entering into such discussion of the more complex and minute phases of the question as is inevitable in a consideration of the relations that exist between the present work and the conceptions of the Traube school, the observations of Kolisko and the experimental work of Mott and of Cannon.

In connection with Mott's work, his findings of increased fluid in the skulls of general paralytics[119] are in accord with the well-recognized tendency of these cases to brain shrinkage and consequent hydrops *ex vacuo*, as already pointed out. It must not be forgotten that brain shrinkage usually implies a widening of the perivascular spaces similar to that seen in senile brains and graphically described by Gowers.[120] Such a condition is frequently encountered at autopsy, and it is not strange that the excessive moisture found on section of the brain should often be erroneously ascribed to a dilatation of those spaces by serum transuded from the blood-vessels. As a matter of fact it seems to be questionable whether dilatation of these "lymphatic" spaces is a possibility. Mott adheres to the view, based on microscopical observations, "that the whole brain is permeated by a canalicular lymph-system containing cerebrospinal fluid, the large processes of the neurons lying in lymph-spaces which are continuous with the perivascular lymphatics."[121]

If these observations are true, then dilatation of the perivascular canals by transudate from contained blood-vessels is impossible, since pressure exerted within them would be readily transmitted by the serum to the surrounding tissue and would therefore be everywhere equal and thus prevent such a phenomenon.

As a matter of fact there is some evidence to show that the perineuronal lymph-spaces are not so readily permeable as is generally believed I have met striking lack of success in attempting to perfuse methylene-blue normal saline solution into fresh brains under varying degrees of

118. The shrinkage in the brains of chronic alcoholics may be explained by the noteworthy changes in the ganglion cells of such cases as taught and demonstrated by Dr. Ira Van Gieson many years ago.

119. Quoted by A. E. Russell, p. 1095.

120. Gowers, William R.: Abstract of a Lecture on The Nervous System in Old Age, Polyclinic, London, 1907, xi, 131.

121. Mott: Arch. Neurol., London, i, 499.

pressure. Whether the apparent impermeability of the brain represents a true finding or whether this failure to demonstrate ready permeability was due to faulty technic or unconsidered factors of capillarity cannot be stated; the technic[122] was similar to that successfully employed by Brodie in demonstrating the permeability of other organs.

I shall not consider Mott's production of edema of the brain in animals by experimental ligation of arteries,[121] since his description shows plainly that his conception of brain edema is widely divergent from that held by the Traube school.

His reference to the ease with which the perineuronal spaces were made out in some of the cases of experimental anemia[121] is of lessened significance when I remind the reader that these appearances are often due to artifacts. Also it must not be overlooked that Huguenin[123] has observed from experiments on animals that a given brain is moister after death than during life.

The essential point to be held in mind in connection with the transudate theory is that pressure continuity exists throughout all the fluid molecules in the cranium. Pressure caused by transudation from the blood-vessels would be transmitted from molecule to molecule everywhere throughout the cranial cavity and spinal canal—it would be felt, generally speaking, as fully or nearly as much in the subarachnoid fluid on the outside of the brain as in that within the perivascular and interstitial spaces. Under these circumstances there would be no disarrangement of the brain, that is to say, no crowding up of the external portions against the bony vault. Nor could there be, as already stated, any measurable molecular compression although intracranial pressure were raised to great heights. Vascular compression would occur, but this would not explain the soggy condition of the tissues (often considerable from the gross and the histological point of view) intervening between the vascular spaces.

On physical grounds therefore we are not justified in maintaining that transudation is a cause of cerebral edema, whatever rôle it may play in the production of edemas elsewhere.[124]

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122. Personal Communication.

123. Huguenin: Handbuch der speziellen Pathologie und Therapie von v. Ziemssen, Suppl. Vol., 1878, p. 6.

124. The following descriptions taken from autopsy report No. 2,402, are interesting since they show that transudation does not necessarily take place within the skull as a result of thrombosis of the veins of the neck.

"Head: The longitudinal sinus is free; there is marked pial edema and a moderate amount of fluid at the base. The cerebral vessels are everywhere thin and normal. The pial veins over both superior convexities are normal with the exception to be noted below. The temporosphenoidal and occipital veins on the surface of the right side are the seat of firm, blackish coagula. On removing the brain, a large vein with its branches filled with blackish clot is found torn and lying on the superior surface of the petrous portion of the temporal bone. This

The old idea propounded by Traube that cerebral edema is due to transudate has persisted with some tenacity in spite of the evidence to the contrary offered by Cannon (1901). With the exception of Cushing (1903 and 1908)[24, 25] it appears that the significance of Cannon's work has been largely overlooked.

Leyden,[125] Duret,[126] Cybulski[127] and Hill[128] all believed that intracranial tension must equal blood tension in order to produce death. Cannon,[129] reasoning from their experiments, in an attempt to explain the mode of death after trauma of the brain; decides that transudation could not raise pressure sufficiently to bring this about, since pressure outside the vessels would not equal that within, owing to loss through resistance of the tissue.

The reader deduces for himself that since the accepted mode of death in cerebral edema is through high tension inducing arterial collapse, the cause of the cerebral edema cannot be transudation.

Cannon develops a theory of edema which differs radically from that of all other observers and in which he ascribes the swelling to osmosis induced by chemical changes in the brain-cells themselves. He finds a satisfactory analogy in the experimental work of Budgett[130] and of Loeb[131] on muscle tissue, and supports his arguments by observations on the capacity of brain tissue when deprived of its blood supply to take up water from a solution isotonic with the blood.[132]

He lays no particular emphasis on causation but points out that Loeb and Budgett emphasized lack of oxygen as a probable cause of the chemical changes in their experiment, and demonstrates the manner in which

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vein evidently formed a communication between the above-named veins and the lateral sinus. The lateral sinus and the bulb on the right side is the seat of a dark coagulum which is markedly adherent to the wall of the vein. The right middle ear contains an excessive amount of clear fluid. The right mastoid cells appear to be mostly closed, the bone being extremely firm and discolored yellowish. The left middle ear and mastoid normal. Cross-section of the brain reveals no gross lesions. There is no edema of the brain substance. The lateral ventricles were not distended and contained a normal amount of fluid.

"Blood-Vessels: The inferior vena cava is normal. The superior vena cava, the right innominate, right and left internal jugular and left external jugular veins are markedly thickened and the seat of an old firmly adherent and partially organized thrombus, which is paler at its cardiac end than toward the head."

125. Leyden, E.: Beiträge und Untersuchungen zur Physiologie und Pathologie des Gehirns, Arch. f. Path. Anat., 1866, xxxvii, 519.

126. Duret, H.: Etude expérimentales et cliniques sur les traumatismes cérébraux, Paris, 1878, p. 183.

127. Cybulski, N.: Zur Frage des Gehirndruckes, Centralbl. f. Physiol., 1891, iv, 834.

128. Hill, L.: The Physiology and Pathology of Cerebral Circulation, p. 168.

129. Cannon: Am. Jour. Physiol., 1901, vi, 101, 102.

130. Budgett, S. P.: The Similarity of Structural Changes Produced by Lack of Oxygen and Certain Poisons, Am. Jour. Physiol., 1898, i, 210.

131. Loeb: Arch. f. d. ges. Physiol., 1898, lxxi, 47.

132. Cannon: Am. Jour. Physiol., 1901, vi, 114, 115.

lack of oxygen would follow as a result of circulatory changes resulting from brain contusion.

Cannon's idea that lack of oxygen sets in motion the processes described, while satisfactory from a surgical standpoint, does not seem to apply equally well to other pathological conditions.

His theory has the merit that it is the only one so far given that is unassailable from the standpoint of mechanics and I cannot but feel that the process described, or something like it, is responsible for all true cases of cerebral edema, meaning by this edema of the brain as distinguished from pial edema.

Cannon[133] suggests a seeming objection to the working out of his theory in the occurrence of fluid noted in the dura or in the ventricles in certain recorded cases; "for why," he says, "does not the fluid pass into the tissues rather than accumulate if the tissues have the great osmotic power attributed to them?" He believes that the question cannot be definitely settled until the osmotic pressure of the fluids has been determined; he adds that the fluids must be encapsulated, and gives the following as a possible explanation:

> The diffusion of salts from the injured tissues into even a slight amount of fluid in an encapsulated space would render that fluid of higher osmotic pressure than the blood-plasma. The plasma would thereupon pass into the encapsulated space in obedience to osmotic laws and thus increase the fluid in its compressing effect. Further change in the injured tissues would lead to greater swelling in them and to diffusion of more of the dissolved products of decomposition. The diffusion into the encapsulated fluid would still further increase its osmotic pressure, and result in still more plasma coming to increase its volume. Thus there would be a passage of salts from tissues to blood in a series of decreasing concentrations, and a passage of fluids to tissues in a series of increasing osmotic pressures. And since water will pass more rapidly than salts through membranes, the result is usually a greater and greater pressure until death supervenes.

The importance of emphasizing Cannon's frank objection to his own theory and his explanation of the same is that if unanswered it affects our own theories and conclusions as well. Such a subdural process as that to which he refers suggests in a way as an analogy, a subdural hydrocephalus—a process in regard to which we know extremely little. Fluid in any amount is so seldom seen post mortem[134] in the subdural space

133. Cannon: Am. Jour. Physiol., 1901, vi, 119.

134. Huguenin has discussed this matter rather carefully. It seems curious that some writers have failed to realize that the cranial subdural space is distinct from the subarachnoid space and its spinal prolongation, for, owing to the close apposition of the membranes, at the foramen magnum, there is no subdural space in the spinal canal. To illustrate my meaning, bloody spinal fluid has been considered to be an evidence of middle meningeal hemorrhage, whereas the presence of blood in this fluid in such cases is only an indication of rupture of the dura and subarachnoid membrane or cerebral laceration. In suppurative internal pachymeningitis the cerebrospinal fluid is clear unless there has been an extension of the process to the pia.

that we seldom expect to come across anything except the yellowish serous fluid that often accompanies a pachymeningitis hemorrhagica interna. Possibly this fluid may not be so readily absorbed as the normal spinal fluid of the subarachnoid space.

More frequently during life the subdural space seems to contain thin exudate of an apparent inflammatory origin, especially where there is middle ear disease. This exudate, or transudate, may or may not represent the incipient stage of a purulent pachymeningitis and has more than once been described by operating otologists as meningitis serosa. Considering these facts, it seems unwise to attempt to draw any conclusions as to why subdural fluid seems to remain in the subdural space in some cases of apparent brain edema when one might naturally expect that it would be squeezed out.

Cannon's explanation as to the action resulting from the diffusion of salts from injured tissues into an encapsulated space, while theoretically sound for dead membranes, ignores the fact that living animal membranes have a selective action permitting the passage of one ion or molecule and preventing the passage of others, and he also appears to overlook the fact that such diffusion would affect primarily the subarachnoid fluid which directly envelops the brain tissue. We actually do not know the mode of absorption of the subarachnoid fluid nor what relation it bears to the subdural fluid, for experiments thus far conducted have not settled this point. Furthermore, were the resorption of the subarachnoid fluid interfered with, the type of swollen brain described by Traube and Kolisko could not occur since its change in volume must necessarily be largely at the expense of spinal fluid.

In regard to the occurrence of accumulations of fluid in the ventricles, of which Cannon speaks,[133] several hypotheses may be offered; first, that the cases mentioned were not those of actually swollen or edematous brains; second, that if they were the edema was in its incipience; third, that there was some obstruction to the outflow of spinal fluid from the ventricles. It is conceivable that under certain conditions of acute brain swelling such a result might be brought about. The oft-described permeability of the brain does not always seem to hold good, for cases have occurred in our experience with apparent sudden onset in which flattened dry convolutions, dry cut section and distended ventricles afforded almost proof positive of a confined and increasing ventricular secretion.

A newer theory of edema than that offered by Cannon and one which applies equally well to intracranial conditions is that recently advanced by Fischer.[135] This theory, built on experiments, assumes that certain alterations in the fluids of the body, as for example too great alkalinity

135. Fischer, Martin H.: The Nature and the Cause of Edema, THE JOURNAL A. M. A., 1908, li, 830.

or acidity (including excess of carbon dioxid) so increases the affinity of colloids for water that they become swollen with resultant edema and swelling of the tissues. Fischer cites as examples of this action of colloids, swellings due to stings of insects, the swelling of gangrenous tissues when water is applied to them, and the swelling of dead bodies kept in water, as cases in point. The brain is rich in colloidal substances which, should they suddenly begin to absorb water,[136] would increase its volume in such a manner as to force all the cerebrospinal fluid from the skull. A subsequent evacuation of a certain amount of fluid into the tissue spaces of the brain, according to the mechanism described by this writer, would give rise to the soggy appearance observed.

While the type of brain of which I have been speaking is undoubtedly the one which Traube's followers have had in mind in their discussions, it is evident that they have now and then (through oversight of a mechanical principle) confused the swollen edematous brain with the more common form in which there is extensive or moderate pial edema and more or less moisture of the brain substance—the type which has been demonstrated as a physiological or pathological brain shrinkage.

In the first place, although it is impossible for the brain and subarachnoidal fluid to be increased at the same time,[137] certain of the cases are so described as to imply that this may have taken place. In Cushing's article[138] in connection with subtemporal decompression in a case of chronic nephritis which has already been referred to, we are told that there was considerable fluid in the subarachnoid space and that the arachnoid membrane was pricked to allow of this escaping. The obvious deduction on reading Cushing's article is that he was dealing with the

136. This theory of colloidal absorption is not generally regarded as proved. It is well known, however, that myelin substances are capable of absorbing large quantities of water.

137. Unless we allow the brains in question to have been markedly shrunken beforehand and admit that they have become swollen since. In such cases we can at least be sure that the edema itself could have played no part in the production of pressure symptoms.

138. On page 488 Cushing describes the operation at this stage as follows: "The dura was exceedingly tense and owing to the marked degree of cerebral protrusion that followed the first incision, it was opened with considerable hesitation in the absence of coincident lumbar punctures. It was accomplished, however, without injury to the pia arachnoid. The subdural space contained no free fluid. *.The arachnoid on the other hand was markedly distended with fluid* which escaped after pricking the membrane in a number of non-vascular spaces where it bridged the exposed sulci. Not only was there a superabundance of fluid in the arachnoid space but the brain itself appeared soggy and wet." This picture it seems is hardly compatible with our conception of the swollen edematous brains described by Traube unless we accept the paradox that in this instance both brain volume and subarachnoid fluid contents were simultaneously increased. The mechanical complications arising as the result of a subsequent cerebral hemorrhage in the right hemisphere (see page 494 autopsy report of same article) certainly renders the case of little value from the standpoint of the study of cerebral edema.

type of brain which has been especially discussed in this paper, and not with a true case of edema of the brain, as he may have supposed.

Similarly Phelps[139] cites a case of a patient dying of traumatic brain injury (the age is not given) in which there was *moderate subarachnoid effusion* and well-marked edema of the brain. Cannon[140] cites this case as an example of brain edema. To multiply such instances is unnecessary.

The conclusion to which we are led, based on the fact that in over 1,000 antopsies taken from the records of the Bellevue Laboratory,[141] there have occurred no truly swollen or edematous brains of the types described either by Kolisko or by Traube, is that these brains are so rare that they cannot figure to any great extent in the common run of those diseases or surgical conditions which they are popularly supposed to accompany and that in many instances the inferences drawn at the autopsy table are incorrect ones based on an improper interpretation of the ordinary appearances of pia arachnoidal collections of fluid, especially where there is also present some widening of the perivascular spaces. It must be remembered, in referring to Kolisko's cases, that the number of autopsies which he has performed is enormous.

Another type occasionally seen is that in which there is general apparent increase in the volume of the brain, diminution in the size of the ventricles, decreased or absent subarachnoid fluid and pronounced flattening of the convolutions; but in none of these cases has there been any increased moisture from the cut surfaces of the hemispheres. On the contrary they have exhibited a rather more than normally dry or glazed appearance.[142]

The relations existing between pial effusions and the appearances described as serous meningitis are such as to create confusion. This is chiefly because the common milky patches on the arachnoid are apt to be mistaken for active inflammatory processes, while any free fluid made out in the subarachnoid space is consequently assumed to be serous unless it is slightly cloudy.[143]

A critical review of the literature of serous meningitis leads one to the conclusion that a great deal has been written on the subject which will not bear analysis; indeed, such an examination causes one to question whether, taking into account the various possibilities of mistake, the

139. Phelps: Traumatic Injuries of the Brain and Its Membranes, vi, 536.

140. Cannon: Am. Jour. Physiol., 1901, vi, 97.

141. Dr. Norris tells me he has never observed this condition, although he has for four years been on the watch for it.

142. A case of this sort is included in our tables of cranial weights and volumes, note Group II, Accession No. 2,099, Table 5.

143. In such cases a careful bacteriological examination must be made to eliminate a beginning inflammatory process, especially in pneumonia.

disease can be said to have been positively demonstrated. Thiemich[144] observes that "the term serous meningitis is primarily anatomical and as such is ambiguous," a statement the truth of which becomes increasingly apparent with added study. The instability of the foundations on which the study of the subject of serous meningitis has been made to rest is made apparent when one analyzes the fourteen cases on which Quincke[145] based his clinical observations. The first six cases were entirely clinical lasting up to five months with acute onset, acute course and recovery. No bacteriological work was done. A second group described as "acute cases with a chronic course," comprises three cases. Two of these came to autopsy and showed chronic internal hydrocephalus with tuberculosis elsewhere in the body.

In a third group comprising five cases and described as "chronic," three came to autopsy. The first of these showed a granular ependymitis with hydrocephalus internus and no tubercles. The second showed chronic hydrocephalus, ventricles very wide and filled with clear fluid, a granular ependyma, meningitis, extensive milky clouding of the pia, and slight opacity of the membranes of the cord. There was a large abscess in the pelvis, pyemic abscesses in the lungs, an old endometritis, and "myelitis (?)." No bacteriological examination was made. In a third case enormous hydrocephalus (800 c.c. of fluid) was present. For the entire group no histological findings are recorded, no bacteriological work was done, and intracranial pressure was measured only five times. Every case of Quincke's, therefore, which came to autopsy, was a case of internal hydrocephalus. It is hard to see on what grounds he based his assumption that in these cases the causative factor was a serous inflammation of the meninges. At the same time Quincke[146] informs us that "he did not find that the fluid in chronic serous meningitis differed from ordinary cerebrospinal fluid. Believing as I do that the spinal fluid is a ventricular secretion,[147] I cannot see how his point is demonstrated or how he differentiates his cases from the ordinary form of internal hydrocephalus.

Thiemich, as already noted, looks on the so-called acute hydrocephalus of childhood as a ventricular serous meningitis. He considers that the fluid of "internal" serous meningitis is usually clear but that there are slight changes which indicate inflammation of the chorioid plexus and ependyma.[148] Possibly the terms "chorioiditis" and "ependymitis" are more suitable here.

144. Thiemich, Serous Meningitis in Diseases of Children, p. 413.

145. Quincke: Samml. klin. Vortr., pp. 656-668.

146. Quincke: Samml. klin. Vortr., p. 678.

147. The reader is referred to Brodie's Harvey Lecture, New York, 1909, on Renal Activity (the chorioid plexus being supposed to functionate as do the glomeruli).

148. For composition of the fluid in hydrocephalus, see under spinal fluid, Text-Book of Physiological Chemistry, Hammarsten Ed., 1908, p. 264.

Quincke makes a statement in his article that has a distinct mechanical significance; he says: "In general venous stasis (as in valvular heart disease) we see, in addition to edema of the brain substance, increase in fluid not only in the ventricles but also, and usually in a higher degree, in the subarachnoid space, whereas local venous stasis leads only to transudation into the ventricles with transudation into the brain and compression of the convolutions against the skull."

Edema of the brain substance with increase in the ventricular and subarachnoid fluids is obviously a mechanical impossibility as already pointed out. The second statement implies a closure of the iter or foramina of Magendie.

Boenninghaus' series is equally as unsatisfactory as Quincke's. It is observed that most of his cases can readily be accounted for as either the beginnings of acute purulent or epidemic cerebrospinal meningitis, or as the chronic and partly healed phases of the same conditions.

It is hard to see how the condition can be demonstrated by the histological findings when we consider that the only way one can really prove that a given case of meningitis is serous in character and not some form of leptomeningitis with brain shrinkage, is by the presence of serous exudate.

Thiemich lays great emphasis on the bacterial, microscopical, and chemical examination of the spinal fluid in these cases and it seems safe to say that this is the only satisfactory method in making a diagnosis.

PART 4.—THE CLINICAL SIGNIFICANCE OF PIAL EDEMA

There are one or two points of importance that require consideration before closing. Of these the first to be considered is the question of the extent to which high intracranial pressure accompanies pial edema.

The simplest method of estimating intracranial pressure post mortem, as has already been stated, is by observation of the tenseness and bulging of the dura just after the skull is opened. Although only a rough guide, this method may be regarded as accurate enough for present purposes. In twenty-eight consecutive cases of pial edema examined, the dura was found tense in ten, indicating that high intracranial pressure coexisted with pial edema in more than one-third of the cases. Proof that the two conditions do not necessarily coexist is furnished by a case of pial edema which was tapped several hours before death by Dr. H. V. Guile, former intern of the Bellevue Hospital staff. The intracranial tension, as measured by him, was normal (150 mm. of H_2O).[149] Certain writers on alcoholism, including some recent ones, have looked on the presence of pial

149. See Accession No. 2,057, in Table 5.

edema as evidence of high intracranial tension; it seems wise in this connection to point out that in many cases symptoms which may have been due to coexistent high intracranial pressure were wrongly ascribed to a "wet-brain" found post mortem.

The second question worthy of attention is, May pial edema be looked on as a cause of symptoms? I have been at some pains to question the various house physicians as to the ante-mortem condition of the cases on which I performed the head autopsies, particularly those cases in which much edema was present. In Table 5 are the results obtained by this system of inquiry.

I give here a report of all cases as they occurred regardless of whether or not edema was present, but regrouped for convenience of study.

TABLE 5.—REPORT OF ALL CASES AS THEY OCCURRED

GROUP 1

Acc. No.	Degree of Edema	Disease	Mental Condition Just Before Death
2,039	XXX	Tuberculous meningitis.	Stupor present.
2,057	XX	Brain tumor.	Stupor present; (intracranial tension ante-mortem was 150 mm. of H_2O).
2,085	XXX	Congenital diplegia ...	Torpid from birth.
2,111	XX	Uremia	Uremic coma.
2,152	X	Tuberculous meningitis.	Stupor present.

In this group are placed those cases in which the nature of the lesion is such that it would be difficult to determine the relation of stupor to the coexisting edema. Case 2,057, mentioned above, is of particular interest as suggesting that stupor with brain tumor is not necessarily dependent on high intracranial tension, as the tension in this case is normal.

GROUP 2.—NO PIAL EDEMA PRESENT

Acc. No.	Degree of Edema	Disease	Mental Condition Just Before Death
1,907	.....	Chronic pulmonary tuberculosis.	No cerebral symptoms.
1,959	.....	Delirium tremens	Delirious till death.
1,974	.....	Polyserositis	No cerebral symptoms.
2,099	.....	Fatty liver; cause of death unknown; infant.	Convulsions.
2,109	.....	Pulmonary tuberculosis.	No pressure or other cerebral symptoms.
2,146	.....	Carcinoma of stomach.	No cerebral symptoms.

The cases in this group have been included merely for the sake of completeness.

Of the following eighteen patients, nine had absolutely no symptoms of cerebral disturbance. Five were irritable or delirious, and four stuporous or comatose. Of the four cases last mentioned, two presented the picture known as "alcoholic wet-brain," a third was profoundly stuporous and a fourth comatose. Although included in this group, it is obvious

that coma in a case of perforated gastric ulcer with fatal hemorrhage (Acc. No. 2,133) might readily be due to other factors than those caused by pressure of fluid on the cortex.

GROUP 3.—CASES SUITABLE FOR STUDY OF THE RELATION OF PIAL EDEMA TO SYMPTOMS OF STUPOR OR COMPRESSION

Acc. No.	Degree of Edema	Disease	Mental Condition Just Before Death
1.879	XX	Cirrhosis of liver.....	No evidence of cerebral disturbance.
1.880	XXX	Interstitial pneumonia.	No signs of cerebral compression.
1.891	XXX	Ac. par. nephritis.....	Had no cerebral symptoms until just before death, when he became slightly delirious and later sank into a stupor about which there was nothing characteristic.
1.892	XXX	Epithelioma of esophagus.	Died in delirium.
1.903	XX	Chronic cardiovascular disease.	Was never comatose, nor did he have any mental symptoms beyond the irritableness common to advanced alcoholics.
1.912	XXXX	General arteriosclerosis.	Characteristic mental symptoms of senility.
1.963	XX	Cardionephritis	No cerebral symptoms..
1.964	XXX	Carcinoma of esophagus	No cerebral symptoms..
2.052	XXXX	Chronic interstitial nephritis.	Stupor was present.
2.082	XX	General miliary tuberculosis.	No cerebral symptoms..
2.113	XX	Chronic alcoholism; gangrenous cervicitis.	Died in delirium.
2.112	XX	Landry's paralysis....	Conscious till death.
2.117	X	Chronic glomerular nephritis.	No cerebral symptoms..
2.133	X	Perforated gastric ulcer.	Died in coma.
2.147	XXX	Pulmonary tuberculosis; chr. alcoholism.	Irrational, wandering and partly stuporous for some time before death.
2.148	XXX	Pulmonary tuberculosis; chr. alcoholism.	Moderate degree of stupor present.
1.949	XX	Secondary hemorrhage.	No cerebral symptoms..
2.153	XXX	Emphysema	Rational all the time; died suddenly on attempting to sit up in bed.

On review, there appears in these findings no evidence in support of the idea that pial edema is in itself a producer of symptoms. The symptoms of delirium tremens and "alcoholic wet-brain," it should be remembered in this connection, have been ascribed more properly by others to toxemia. My observations thus have led me to believe that such symptoms as have been recorded are the result of high intracranial pressure or toxemia (CO_2 or other poisons), or both, coexisting with pial edema, but not otherwise related to it.

CONCLUSION

My conclusions may be summed up as follows:

1. The collection of fluid in the pia mater is not *per se* a pathological process but in every instance represents the reciprocal of brain shrinkage.

2. It produces *per se* no symptoms.

3. Thickenings of the meninges in such cases take place chiefly in the arachnoid and are not to be regarded as representing a true inflammatory process.

4. The brain increases in size up to puberty and diminishes thereafter proportionately to its diminution in weight, as shown by comparison with the tables of brain weights presented.

5. Increase or diminution in size of the brain is not determined by the state of nutrition of the rest of the body.

6. The appearance of "wet-brain" so called, or pial edema of alcoholics, is due to brain shrinkage and has no pathological significance *per se*.

7. The appearances of pia-arachnoidal effusion are readily mistaken for those of serous meningitis.

8. When a collection of fluid is present in the pia arachnoid, a diagnosis of edema of the brain is open to question and can be made only on the assumption that the brain has been previously in a more shrunken condition.

9. We see no reason to believe that transudation can be a causative factor in the production of cerebral edema.

10. Cases of swollen or edematous brains with dry pias are decidedly uncommon at autopsy and the diagnosis of cerebral edema should be made only when actual increase in the volume of the brain matter can be proved.

I wish to thank Dr. Charles Norris for the opportunity to carry out these investigations and for his extended cooperation and criticism. I also wish to thank Drs. A. M. Pappenheimer and Cyrus W. Field of the laboratory staff for assistance and criticisms; Dr. Ernest Sachs for a critical review and Mr. Albert L. Stillman for an exposition of those principles of mechanics and physics that are involved in this paper.

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A CLINICOPATHOLOGICAL STUDY OF PRIMARY CARCINOMA OF THE LIVER*

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Although much had been written previously, the work of Hanot and Gilbert[1] was the first comprehensive investigation of primary carcinoma of the liver and marked a distinct epoch in the study of the disease. Numerous contributions followed this before the publication of Eggel's[2] great work, the most notable in the interim being that of Siegenbeek van Heukelom[3] whose brevity, clearness and penetrating logic demonstrated a most comprehensive grasp of the subject.

It is not my purpose to go into the details of the voluminous literature on primary carcinoma of the liver, for the works mentioned are most painstaking in this respect. Furthermore some of the more recent essays on the subject bring the literature completely up to date; among these works should be mentioned the writings of Conti,[4] Fulci,[5] Bertelli,[6] Theodorow,[7] Ribbert,[8] Cruickshank and Teacher,[9] and of Fabiani.[10]

In order to have some standard for judgment I have accepted Eggel's conception of the clinical and pathological features of the disease, for although several years have passed since the appearance of his paper, very little is to be added to his description. After reviewing the literature of the nomenclature of epithelial tumors he includes under the broad term of carcinoma all epithelial new growths of malignant character, a thoroughly German conception. In reference to the liver, he speaks of carcinoma when there is either macroscopically or microscopically the formation of tumor thrombi or metastases or when there is exhibited a destructive influence on the surrounding liver tissue.

On the basis of Eggel's critical study of 163 cases from the world's literature it may be said that cancer of the liver is most frequently a

*From the McManes Laboratory of Pathology, University of Pennsylvania.
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1. Hanot and Gilbert: Etudes sur les maladies du foie, Paris, 1888.
2. Eggel: Beitr. z. path. Anat. u. z. allg. Path., 1901, xxx, 506.
3. Siegenbeek van Heukelom: Beitr. z. path. Anat. u. z. allg. Path., 1894, xvi, 341.
4. Conti: Policlinico, Rome, 1908, xv, 385.
5. Fulci: Policlinico, Rome, 1908, xv, 408.
6. Bertelli: Riforma Med., 1908, xxiv, 957.
7. Theodorow: Virchow's Arch. f. path. Anat., 1908, excii, 407.
8. Ribbert: Deutsch. med. Wchnschr., 1909, p. 1607.
9. Cruickshank and Teacher: Jour. Path. and Bacteriol., 1910, xiv, 282.
10. Fabiani: Gaz. d. osp., 1910, xxx, 433.

disease of men (63.3 per cent. males, 36.7 per cent. females) occurring particularly between 50 and 60 years of age (average for men 53.11 years, for women, 52.23 years). The past history of the patient often shows factors that would seem to favor cirrhosis, such as alcoholism, syphilis, biliary calculi, trauma and in a few cases (four in 163) a history of cancer in other members of the patient's family.

Clinically, the earliest symptoms are those of more or less vague trouble in the gastro-intestinal tract. Before the appearance of the symptoms referable to cancer, symptoms of atrophic cirrhosis sometimes predominate. After the development of the cancer, loss of flesh, digestive disturbance and cachexia put in their appearance. Statistically the 163 cases show icterus in 61 per cent., ascites in 58.5 per cent., edema, especially of the lower extremities, in 41 per cent., splenic tumor in 32 per cent. and fever in 14 per cent. The duration averages about six months, although the estimation of the time of origin is much confused by the symptoms of the early cirrhosis.

From the point of view of gross morbid anatomy Eggel differentiates three forms of primary carcinoma of the liver:

1. The nodular form. The new growth appears in the form of nodules of variable number and size, for the most part clearly separated from the liver tissue.

2. The massive form. The tumor forms a large mass taking in an entire lobe or the greater part of it, is poorly defined and often shows smaller metastatic nodules.

3. The diffuse form. The whole liver is infiltrated with numerous small tumor nodules often no larger than an acinus, each enclosed in a connective tissue band so that the liver often is only differentiated from a pure cirrhosis by the aid of the microscope.

This grouping differs from the generally accepted classification of Hanot and Gilbert only in the third form, which the latter authors term *cancer avec cirrhose*. Cirrhosis is such a common feature in cancers that should properly be classified as nodular or massive, that in the light of more modern studies of a greater number of cases, this classification of Hanot and Gilbert seems unjustified.

Microscopically there are two chief groups, the carcinoma solidum (really a carcinoma simplex) and the carcinoma adenomatosum, corresponding respectively to the *épithéliome alveolaire* and the *épithéliome trabéculaire* of Hanot and Gilbert.

Although Hanot and Gilbert thought it possible to differentiate these forms clinically, the studies of Eggel and others seem to indicate the impracticability of such a fine diagnosis.

The purpose of the present communication is to present a detailed study of nine cases of primary carcinoma of the liver, some of which came under my personal observation in the Philadelphia General Hospital

and the University Hospital, and others of which were kindly referred to me by Dr. Warfield T. Longcope, the Director of the Ayer Clinical Laboratory of the Pennsylvania Hospital. The special features of these cases will be discussed with their individual presentation. The gross descriptions of the specimens from the Pennsylvania Hospital are by Dr. Longcope. The minute descriptions throughout are my own.

REPORTS OF CASES

CASE 1.—*History.*—M. W., a white woman, aged 40, was a patient in the University Hospital (No. 1,885) in the service of Drs. Martin and Carnett. The clinical history is abstracted as follows: The family history is negative. Eighteen years ago the patient had an attack of chills, fever and jaundice with vague pains in the abdomen; she had similar attacks about once a year from this time on, and the most of these had the same symptoms with loose light-colored stools. She never vomited but often felt nauseated. Seven years ago she had an attack of inflammatory rheumatism which lasted four weeks. She has been an excessive coffee-drinker.

Present Illness.—Three months ago the patient was taken with an attack of chills, fever and jaundice, the last being much deeper than ever and remaining unchanged up to the present time; has much diarrhea, has lost weight and complains now of pain and tenderness in the upper abdomen, especially on the right side.

Physical Examination: Jaundice and emaciation are present and the liver is markedly enlarged, easily palpable, as is also the case with the spleen. Temperature is not elevated at any time. Urine shows slight sediment, 1.018, acid, negative for albumin, sugar, but positive for bile; it shows a few leukocytes and epithelium.

Blood: Hemoglobin, 71 per cent.; red blood-cells, 3,910,000; white blood-cells, 7,900. Differential count, polymorphonuclears, 70 per cent.; lymphocytes, 12 per cent.; large mononuclears 1 per cent.; transitionals, 9 per cent.; eosinophils, 6 per cent.; basophils, 2 per cent. No malarial organisms.

Stools show no free fat, but a few fatty acid crystals, a few small masses of soap.

Exploratory operation was performed by Dr. Martin after which there developed a very marked hemophilic condition and the patient died a few days later.

Necropsy (by H. T. K.).—This was performed about twelve hours after death. The notes are abstracted as follows: Liver weighs 2,320 gm.; measures 28 by 23 by 7.5 cm.; shows prolongation of the sharp anterior edge; the edge itself is of normal sharpness. The upper surface is flattened. The capsule is adherent posteriorly and there are several glands adherent but not very densely, in the transverse fissure. The surface of the liver is coarsely granular but, except in the position of adhesion, shows a glistening surface. The color is generally green with mottlings of yellow and yellowish-gray areas approximating the size of a millet-seed to that of a small pea; consistence is greatly increased. On section the liver cuts with considerably increased resistance; cut surface shows the same degree of granularity as noted on the outer surface. In a few areas tubules with very much thickened yellowish-gray walls are seen to be cut across. Approaching the under surface of the right lobe one finds on cross-section a mass running almost directly anteroposteriorly, apparently spindle-shaped, extending from the anterior margin of the liver almost all the way through it, but not being visible on the surface except anteriorly where a small area of triangular shape is seen, which superficially resembles scar tissue. A cross-section of tumor mass in its middle part measures 5 by 3 cm.; it tapers posteriorly to become invisible, while anteriorly it measures roughly 2 cm. in diameter. Direct connection of one part of this mass with other parts all through the liver sub-

stance cannot positively be demonstrated. The mass is not sharply outlined and fades away into the hepatic tissue with almost no signs of pressure, apparently replacing the parenchyma. The tumor is grayish-yellow in color with some pin-head points centrally placed of a deep yellow color with a peripheral zone of hemorrhagic points varying from bright red to a deep blue color. The consistence of the mass is somewhat firmer than that of the liver tissue and approximates that of hard rubber; the central minute yellowish areas are considerably softer and are probably minute areas of necrosis. The number of ducts with thickened walls (same hard consistence as tumor) is greater in the neighborhood of the tumor than in other parts of the liver, but can be demonstrated generally in both right and left lobes.

The condition of the other organs is indicated in the gross anatomical diagnosis as follows: Primary carcinoma of liver, metastases to subhepatic glands and right adrenal; general jaundice, ascites, splenic tumor; chronic diffuse nephritis; general abdominal congestion; laceration, erosion of cervix uteri with hemorrhage into wall; chronic adhesive perioophoritis (left); chronic cystic oophoritis (right); edema and congestion of lungs; very slight cloudy swelling of myocardium. Microscopically, three sections from the liver were studied, one of liver, two of tumor. The liver proper shows marked thickening of the capsule of Glisson made up of moderately dense fibrous tissue without many nuclei but considerably infiltrated with round cells. In many places the capsule is infiltrated with epithelial cells of the type of those found in the tumor, i. e., large, generally circular vesicular nuclei and moderately abundant, well-stained protoplasm. Many epithelial tubules are seen on cross-section which either appear as normal gall-ducts, or show several irregular layers of epithelium without distinct basal membrane. Some of the larger bile-ducts show distinct peripheral fibrosis. The blood-vessels are normal. In many areas the peripheral parts of the lobule show distinct replacement of the liver-cells by irregularly placed cells of the type seen in the tumor. The parenchymal cells are swollen, granular and show loss of outline although the general chain arrangement is maintained. Many of the cells contain masses of granular greenish-yellow pigment which in some cases is so abundant as to completely occupy the cell. In many cases large collections of pigment are found in spaces corresponding to bile capillaries. The nuclei are generally normal, some few, however, stain poorly and show abnormal arrangement of chromatin. Duplication of nuclei in a cell is observed but no mitotic figures. Central veins show no congestion.

The tumor proper is richly fibrous and is made of irregularly arranged intercommunicating acini, lined sometimes by a single layer, sometimes by multiple layers of epithelial cells. These are low columnar cells, morphologically and tinctorially like bile-duct epithelium, often, however, being of somewhat larger size. The nuclei, frequently, are more highly vesicular than in normal ducts and mitotic figures are fairly frequent. The growth penetrates through the liver tissue irregularly, in places substituting itself for liver tissue and in other places pushing the tissue aside. Numerous areas show fine hemorrhages. There appears to be every transitional stage between simple bile-duct proliferation and the adenocarcinoma. Extension into veins occurs but is not frequent; the tumor even here shows the adenomatous arrangement and often completely obliterates the vessel. Involvement of lymph-spaces could not be determined.

Other tissues were examined microscopically, the diagnosis being: Primary adenocarcinoma of the liver, with involvement of the liver veins; cloudy swelling of myocardium, chronic congestion of spleen; chronic interstitial nephritis with superimposed acute parenchymatous nephritis.

To summarize, the tumor appeared in a woman 40 years of age. Clinically she had a history of excessive coffee-drinking, and an illness simulating cholelithiasis. She showed jaundice, emaciation, and very slight ascites. Pathologically the tumor was primary in the liver, with limited

metastases, slight neoplastic thrombosis, cirrhosis and splenic tumor. The liver tumor is of the tubular type and apparently has its origin in the finer bile-ducts.

CASE 2.—*History.*—C. C., a Swedish man, aged 49; was a patient in the Philadelphia General Hospital (No. 2,450) on the service of Dr. H. B. Allyn. The clinical history is abstracted as follows: The chief complaint is weakness in both legs. The family history is negative. The patient had the usual diseases of childhood; had pneumonia, had lead colic five years ago. He does not use alcohol; denies venereal infection. He is a lead worker. The present illness began with pain in the abdomen, weakness and constipation one week ago.

Physical Examination.—This shows blue line on gums, arcus senilis, unequal pupils, enlarged liver (3 cm. below costal margin) and later demonstrable ascites. Before death he developed convulsions, hematemesis, delirium.

Blood: Hemoglobin, 40 per cent.; erythrocytes, 3,230,000; leukocytes, 5,000, of which the polymorphonuclears formed 76 per cent., small lymphocytes, 9 per cent.; large lymphocytes, 8 per cent.; eosinophils, 3 per cent., basophils, 4 per cent. No basic degeneration of erythrocytes.

Urine: Alkaline, specific gravity, 1.018; negative for albumin and sugar.

Necropsy.—This was performed by me twenty-four hours after death, the notes being abstracted as follows: Liver weighs 3,300 gm.; measures 28 by 23 by 11 cm.; very firm, abnormally rounded, shows a smooth, glistening, transparent capsule through which the liver substance is seen to be studded with innumerable grayish-yellow nodules with umbilicated surface, generally rounded, discrete and confluent, varying in size from a diameter of 1 mm. up to 4 cm. The organ cuts with moderately increased resistance, shows the same appearance of discrete and conglomerate nodules, showing a central mass of bright yellow structureless apparently necrotic material sharply outlined, and surrounded by a linear pearly gray mass generally about 2 mm. in thickness; this latter mass, although sharply outlined from the central necrosis, is not sharply defined from the liver substance and shows a tendency to diffuse itself through the liver substance following in a general way the lines of the capsule of Glisson. In some places suggestions of liver structure are still found within the central necrotic masses and some of these also show small areas of hemorrhage. The uninvolved liver tissue is very small in amount and shows well-marked central congestion and greenish-yellow discoloration of the peripheral zone.

The other organs correspond in appearance to the gross anatomic diagnosis: Primary nodular carcinoma of liver with metastases to lungs, pleuræ, pancreas, left kidney, retroperitoneal lymph-nodes; congestion and edema of lungs; ascites (4 liters); anemic infarcts of spleen and kidneys; acute vegetative mitral and aortic valvulitis; chronic interstitial nephritis; arteriosclerosis.

Microscopically the description of the liver is the composite of five slides. Capsule thickened by an overgrowth of dense fibrous tissue. The capsule of Glisson shows well-marked fibrous tissue overgrowth and some lymphocytic infiltration. The veins are moderately congested and the arteries show slight thickening of their walls. In numerous places where there is especially marked overgrowth of the fibrous tissue an epithelial proliferation is noted. The epithelial cells are columnar type and are arranged in the form of irregular tubular or acinous masses, either solitary or continuing to form large infiltrating areas. In one slide the cells correspond very closely to those of the bile ducts, being low columnar, only moderately acidophilic, and with relatively small, circular, slightly vesicular nuclei. In studying the sections considerable variation is noted in the character of the epithelial cells of the proliferating masses, those showing most marked change being of high columnar type, with suggestions of cilia, faintly stained protoplasm and vacuoles which, although usually small and poorly defined, contain a finely granular basically stained substance evidently mucinous in nature. Much of the epithelium of this type is mounted on thin villous strips of

connective tissue. In the places where the cells present a less markedly columnar element there can be found occasional figures, which present the same type of proliferation as that seen in the coccidiosis of the rabbit's liver—a surrounding band of connective tissue and a distinct villous proliferation of the lining epithelium. The tumor as a whole shows few karyokinetic figures. The lumina of the acini are more or less filled with slightly acidophilic granular material and fragments of nuclei, in some instances also complete desquamation of the cells; the supporting connective tissue is scanty. Evidences of infiltration are numerous. Piling up of cells along the walls of the acini and definite penetration of the basement membrane are seen commonly. Penetration of the mass through the liver substance replacing connective tissue and substituting itself for parenchymal tissue is a common feature. Necrosis is found in several sections, apparently as a central change, the necrosing areas being surrounded by proliferating epithelial tissue. Small areas showing neoplastic thrombosis of the perilobular veins are observed but they are relatively infrequent.

The lobules not involved by the cancer show swelling of the parenchymal cells, obliteration of outline, obscuration of the nuclei and protoplasmic granularity. The nuclei are vesicular but variable in size, some being much enlarged and showing increased chromatin content. Many of the central lobular cells show minute vacuolization, associated with slight nuclear pyknosis and some hemosiderin pigmentation. Fibrosis about the central vein can be seen but no congestion is noted.

Other organs were examined microscopically and the diagnosis is as follows: Primary adenocarcinoma of liver with neoplastic thrombosis of veins; passive congestion, edema, tumor metastases of lung; slight chronic interstitial myocarditis and infarct of papillary muscle; chronic fibrous splenitis and perisplenitis, anemic infarct of spleen; subacute parenchymatous nephritis, anemic infarct, tumor metastases; slight vacuolation and chromaffine increase in adrenals; tumor metastases of lymph-node.

To summarize, this tumor appeared in a man 49 years of age. Clinically there is a history of lead-poisoning (lead worker), short duration of illness, ascites, enlarged liver, abdominal pain (possibly lead colic) but no jaundice. Pathologically the tumor is of the nodular type with very little cirrhosis, histologically adenomatous, with slight neoplastic thrombosis and wide-spread metastases outside the liver.

CASE 3.[11]—*History.*—The patient, E. F. (No. 2,128), was a girl aged 11, white. Section was submitted to the laboratory through the State Department of Health by Dr. H. Y. Pennell, of East Downingtown, Pa. Dr. Pennell in a letter gave the following history, which has been abstracted: The patient was of exceptionally robust stock, the history being otherwise negative. She had always been strong and healthy except for an attack of pneumonia eight years ago.

Present Illness.—This began early last summer. The patient consulted a physician in June, 1907, and following months for jaundice. This (jaundice), with loss of energy and disinclination to work or play or walk far, was the chief symptom, until within the last two or three months. It was recently noticed that she had become unnaturally stout and so weak that she could with difficulty go upstairs. She complained of no pain excepting over the heart on exertion.

Physical Examination.—This showed cachectic pallor, moderate jaundice, ascites, distention of abdominal veins, hypertrophied heart, dyspnea, anasarca. The temperature ranged between 99 F. and 103 F., pulse about 130, respiration

11. This case was used by me in a paper on Carcinoma in Early Life, New York Med. Jour., 1909, xc, 1109.

about 34. Feces were pale; urine negative for albumin and sugar. Blood examination failed to show leukocytes. Constant systolic apical cardiac murmur.

Necropsy.—This was limited to the abdomen, and was performed by Dr. Pennell, whose notes are abstracted: "On opening the median line of the abdomen the first thing met was the enlarged spleen, about the size of a normal liver, very dark and uniform in color, soft and smooth. . . . The liver was next investigated and found to be of a brownish yellow color, a little smaller than normal, very hard, and containing on the surface and within the substance innumerable tumors, of size from those just visible to that of a walnut. The larger ones showing radiations from umbilicated centers. It was a portion of one of these sent for examination. The gall-bladder was empty, normal in size, but almost pure white in color. The stomach and bowels, as also both kidneys and pancreas, appeared to be normal. There was no tumor in the pelvis. I regret not having examined the heart and mediastinum, but was convinced at the time that we had the primary seat of trouble in the liver."

Histologically, the section of liver showed the perilobular connective tissue much increased and the seat of numerous fibroblastic and other early cellular elements indicating the progressive character of the cirrhotic feature of the case. All through this tissue were found small biliary tubules, and scattered in the structure were small, isolated groups of hepatic cells which had been cut off from the lobules by the invading connective tissue. In addition there were scattered numerous smaller epithelial cells of the type of the bile-ducts, both as isolated cells and in more or less broken columns. The fibrous tissue penetrated to some extent into the hepatic lobules, but in very irregular manner and degree.

The hepatic tissue showed a variable state; at places (generally rather toward the periphery than center of the lobule) it was definitely necrotic or showed fatty degeneration. Much showed a minor grade of fatty infiltration, and much was practically unchanged. No pigmentary deposits were noted, either in the liver cells or in the perilobular tissue.

The general appearance was that of an adenocarcinoma, apparently quite diffuse, and accompanied by a progressive cirrhosis.

The spleen showed congestion and edema.

To summarize, this tumor appeared in a girl aged 11, whose history is negative. She showed a short duration of disease, jaundice, ascites, edema clinically; and a nodular adenocarcinoma of the liver with cirrhosis but without venous involvement or apparent metastasis.

CASE 4.—*History.*—F. W., a white man, aged 53, an American, was a patient in the Philadelphia General Hospital (No. 2,518), on the service of Dr. Henry. The clinical notes are abstracted as follows:

The chief complaint is pain and tenderness in the epigastrium. The family history is negative. The patient had the usual diseases of childhood; he used tobacco excessively, never used alcohol to excess. The present illness began with pain and tenderness in epigastrium two months before admission. The patient had hemoptysis occasionally.

Physical Examination.—This shows slight jaundice of upper part of body, dilated veins of chest, nodular enlargement of liver, ascites, splenic enlargement, edema of feet.

Blood: Hemoglobin 70 per cent.; erythrocytes, 3,560,000; leukocytes, 8,800, of which polymorphonuclears formed 67 per cent., small lymphocytes 26 per cent., large lymphocytes 1 per cent., eosinophils, 4 per cent., basophils, 2 per cent.

Urine: Acid, specific gravity 1,026, shows erythrocytes and epithelial cells, negative for albumin and sugar.

Stools: negative for occult blood.

The patient died of erysipelas.

Necropsy.—This was performed by me thirty-six hours after death, the notes being abstracted as follows: Liver weighs 2,700 gm.; measures 31 by 18 by 9 cm.; surface markedly irregular and nodular, deeply blood-stained and markedly adherent to the omentum, which is folded over the surface of the liver. Through the capsule many of the nodules have a yellow appearance and others show a dark red color; none show umbilication. Organ cuts with increased resistance and in the right lobe it measures only 12 cm. in coronary diameter, shows a well-marked atrophic cirrhosis, there being present a dense network of fibrous tissue in whose meshes are circular masses of slightly projecting greenish brown liver substance. The left lobe is enormously enlarged in all its diameters and shows little remaining liver tissue. Cross-section shows necrotic nodules varying from a diameter of 1 mm. up to 5 cm.; the edges are not sharply outlined and tend to fuse with irregular bands of connective tissue about them. These nodules, which show red through the capsule, appear to be made up of a small network of distended vessels.

The other organs showed the appearances indicated in the gross anatomical diagnosis: Chronic adhesive pleurisy, passive congestion and edema, tumor metastases, of lung; cloudy swelling of myocardium, sclerotic mitral and aortic valves; primary cancer, with atrophic cirrhosis of liver; acute splenic tumor and chronic fibrous perisplenitis; arteriosclerotic chronic interstitial nephritis; chronic atrophic gastritis; congestion of gastro-intestinal tract; ascites; arteriosclerosis; tumor metastases to mediastinal, retroperitoneal and mesenteric lymph-nodes.

Microscopically several sections of liver were examined. The outer capsule and perilobular connective tissue are considerably overgrown and show slight infiltration with lymphocytes. The overgrowth is so marked that the acini of the liver appear as small isolated masses scattered irregularly throughout. The liver-cells show cloudy swelling and in the center of the lobule considerable atrophy. The central veins are moderately congested. Marked bile-duct proliferation is evident throughout. The veins of the perilobular tissue are considerably congested and show frequent neoplastic thrombosis.

The tumor is made up of low columnar and irregular cells approximating the size of those of the bile-ducts, and the staining reactions of the protoplasm are closely similar. The nuclei are small, vesicular and very like those of the bile-ducts. Mitotic figures are very infrequent. For the most part these cells are arranged in fairly large nests with ramifications into the surrounding tissue in the form of small finger-like projections. The cells in the margins of these masses are well preserved, but there is very evident central necrosis and frequent microscopic hemorrhage into these necrotic areas. The invasion of the veins is very well marked, the vessels being completely occluded by the thrombotic masses and showing some stretching of the muscular and elastic tissues of their walls. Connection between the larger masses and the proliferated bile-ducts is not very clear but transition stages can be demonstrated with great facility. The finer grouping of the cells of the larger masses is not clearly adenomatous because of the fact that, although the cells are arranged in little circles, yet distinct lumina are infrequent. However, the grouping of the cells and their apparent connection with, and close similarity to, the proliferated bile-ducts seems to justify the diagnosis of tubular adenocarcinoma.

Sections of other organs were made, the microscopic diagnosis being: Primary adenocarcinoma of liver with marked sclerosis and neoplastic thrombosis; metastasis to diaphragm, lungs, lymph-nodes (mediastinal); passive congestion, edema of lungs; leukoplakia of tongue; chronic interstitial splenitis, pancreatitis, nephritis; fibrosis and chromaffin increase in adrenals.

To summarize, this tumor appeared in a man 53 years of age. The history shows excessive use of tobacco, short duration of illness, ascites, hemoptysis (?), dilated veins of chest, nodular enlargement of liver,

splenic enlargement, ascites, edema of feet and slight jaundice. Pathologically, the tumor is notable for its marked fibrosis associated with general cirrhosis elsewhere. The tumor is nodular in type, glandular microscopically, shows neoplastic thrombosis, moderately rich metastasis and associated splenic tumor.

CASE 5.—*History.*—The patient, J. K., a white man, aged 52, American, was in the service of Dr. Stengel in the Pennsylvania Hospital (No. 1,154). The records and specimens were furnished me by Dr. Longcope. A brief abstract of the clinical history follows: The chief complaint is pain in abdomen. Past history is negative, except for alcoholism.

Present Illness.—Symptoms began four months ago with cramp-like pains in abdomen. Three weeks ago the patient became jaundiced and began to vomit; he had constipation and clay-colored stools; there was no blood in stools or vomitus. The abdomen increased rapidly in size. Recently the legs were edematous.

Physical Examination.—The patient is emaciated and jaundiced, with coated tongue; no enlargement of lymph-nodes. Temperature is subnormal; pulse and respiration normal; lungs and heart negative. Abdomen shows constriction at costal margin, prominent wave present; no movable dulness; veins engorged about flanks. Liver is 3 cm. below costal margin in nipple line. The spleen is negative. The urine is deep brown, flocculer sediment, acid, no albumin or sugar.

On the day before death an exploratory laparotomy by Dr. Hutchinson was followed by the escape of 6 or 8 pints of clear yellow fluid. The gall-bladder found to be distended but not inflamed and free from stones. There were four or five hard lumps about the common duct which on incision seemed to be involved glands. Over the dome of the liver nodules were found. The head of the pancreas and pylorus were free. There were a few adhesions between the gall-bladder and intestines. The patient died shortly after this and the necropsy was performed through the operative incision by Dr. E. B. Krumbhaar, twenty hours after death. His notes are abstracted as follows:

Necropsy.—The abdomen contained 500 c.c. of thick bloody fluid. The general description of the abdominal cavity corresponds to that found at operation. The liver weighs 1,530 gm.; measures 25 by 19 by 9 cm. It is of normal shape and consistence and an olive-green color in which bright streaks of reddish purple are visible. The capsule is not thickened, but occasionally light yellow circumscribed spots are visible over the surface. These areas have a definite outline, are sometimes irregularly circular, sometimes elliptical and sometimes very irregular. They feel somewhat softer than the surrounding tissue and are very slightly depressed. The cut surface of the liver shows fairly distinct lobular markings with yellowish-green peripheral zones and olive-green central zones. The areas described on the surface are found to extend several millimeters into the liver tissue. On the surface there are also found bright reddish-purple streaks which in the cut section are seen to extend diagonally deep into the liver tissue like veins in marble. At the junction of the two lobes a striking picture is presented of dilated bile-stained veins surrounded by yellowish margins which quite replace the normal liver tissue. These masses in places are quite hard and firm and in other places comparatively soft. They gradually infiltrate the liver structure and occasionally greenish islands can be seen isolated in the yellowish mass. On dissecting out the common duct it is found to be patulous, though at one place it shows a ragged wall connecting it with the green stained connective tissue mass. The cystic duct is patulous and bile readily flows from the gall-bladder to the duodenum. The hepatic duct, however, shortly before its junction with the cystic duct is found to be invaded by the yellowish growth before described, so that it is impossible to pass a probe any distance into the liver. The lymph-nodes at the hilum of the liver are enlarged and made up of resistant elastic yellowish tissue.

The description of the various organs corresponds to the gross anatomical diagnosis: Primary tumor of liver causing obstruction of hepatic duct and hepatic veins; general icterus and emaciation; multiple infarcts (?) of liver; metastases of tumor to pleura and mesentery and retroperitoneal lymph-nodes; congestion, edema and partial atelectasis of right lung and intestinal peritoneum; cloudy swelling of kidneys; chronic cholecystitis; healed tuberculosis of lungs.

Microscopically, sections from the liver taken where the tumor involvement is not especially marked show an outer capsule of normal thickness, and a perilobular capsule which is distinctly overgrown. The tissue is loosely arranged and with the Weigert stain shows a moderately rich elastica. The blood-vessels show little change except for the presence of well-marked venous stasis and an occasional venous thrombus. None of the thrombi show the presence of tumor elements. The bile-ducts are definitely increased in number and occasionally show clubbing at their ends or other irregularities to suggest beginning atypical proliferation. The cells of the parenchyma show advanced cloudy swelling throughout and in addition those placed centrally in the lobules are distinctly atrophic, more markedly degenerate and in places distinctly necrotic. The central vein is congested, and with the Mallory connective tissue stain perivenous fibrosis running out between the necrotic cells is very well marked.

The sections taken from tumor proper show small areas where the picture is the same as that described above, but the greater part of these sections show dense connective tissue masses containing a few smooth muscle bands and richly infiltrated with an epithelial overgrowth showing itself in the form of small acini which sometimes are lined by columnar cells like those of the bile-ducts, sometimes by larger cuboidal cells with relatively large vesicular nuclei and occasionally seen as irregular masses of irregularly hexagonal cells showing no lumen whatever. In some fields masses of this sort appear as terminal bulbs attached to the smaller tubular acini. Mitotic figures are fairly numerous. The lumina of many of the acini are filled with a finely granular faintly basophilic material, evidently mucin. The entire mass, both epithelium and connective tissue, appears to substitute itself for liver tissue, the parenchymatous cells undergoing more or less marked necrosis in the neighborhood of the advancing growth. Areas are found with changes intermediate between the moderate bile-duct proliberation of the first section and the distinctly malignant growth of the second section and from this point of view it would appear that the growth is from the bile-ducts. In other places there appears to be direct transformation from parenchymatous cells into cancer-cells, but this appearance might easily be the result of the invasion of the tumor mass. Venous thrombosis is present in these sections but no cancer-cells are observed in the thrombi. Granules of bile-pigment are observed in the liver lobules in all sections but no evidence of it is seen in the tumor.

Sections from other viscera were examined and the microscopic diagnosis in full reads: Brown atrophy of myocardium and fibrosis of the mural endocardium; congestion and caseous tuberculosis of lungs; primary adenocarcinoma of liver with metastases to pleura, peritoneum, mesentery, retroperitoneum, pancreas, adrenal and lymph-nodes; moderate perilobular cirrhosis, cloudy swelling, biliary pigmentation and passive congestion of liver; cloudy swelling of kidney.

To summarize, this case is one of primary adenocarcinoma of the liver probably originating in the finer bile-ducts, in a man aged 40. Clinically the course was short; there was a history of alcoholism; icterus, ascites, and edema of the legs were present. Pathologically, the features were the presence of the primary growth associated with cirrhosis and fairly wide-spread metastases.

CASE 6.—*History.*—M. N., Chinaman, aged 50, was a patient in the Pennsylvania Hospital, in the service of Dr. Newlin (No. 1,137). The autopsy was per-

formed by Dr. Longcope, who furnished me with the specimens and records. An abstract of the clinical history follows:

The chief complaint is diarrhea and fulness in the abdomen. Temperature, 97; pulse, 92; respiration, 24, on admission. The patient has never been sick more than a day or two at a time until the present illness; has lost weight gradually for ten years; smokes opium.

Present Illness.—The patient has been sick two months; the abdomen has been swollen three weeks. The patient has had pain in hypochondrium two weeks. His appetite is poor.

Physical Examination.—The patient is emaciated; jaundiced; marked arcus senilis; tongue dry, coated. Abdomen distended and contains fluid. Liver and spleen not palpable. Slight edema of feet and ankles.

Urine: Clear, deep amber, acid, 1.031, no sugar, trace of albumin, contains bile, cylindroids.

Blood: Hemoglobin, 75 per cent.; leukocytes 11,200; red blood-cells, 4,340,000.

Stools show occult blood.

The patient became delirious before he died.

Necropsy.—The abstract of the notes is as follows: Gall-bladder contains more than 100 c.c. of dark greenish-brown bile; its wall is thin and the mucous membrane is grayish in color. Cystic duct is patulous. Hepatic duct is slightly dilated as it enters the liver and its course cannot be followed very far. Both ducts contain a small amount of soft reddish-gray material.

Mesenteric veins are blocked by the same material.

Liver weighs 1,850 gm.; measures 30 by 16 by 9 cm.; it is dark grayish yellow in color mottled by yellowish white to dark green elevated areas measuring from a pin head to 1 cm. in diameter. Elevations are numerous and very irregular in shape and distribution; the yellowish-white elevations are more numerous in the left lobe and the greenish ones in the right. These elevations are glistening but the tissue separating them is opaque. In the right lobe, either anteriorly or posteriorly, the greenish-gray and brownish-red elevations predominate except around a cicatricial band of white, hard tissue 12 cm. in length, which starts at the junction of the lower border of both lobes and goes upward and backward; this shows many yellowish-white elevations. On section the liver is very flabby, and green to yellow in color; lobulation is obscured, but at the upper portion of the dome a few greenish-yellow lobules can be seen surrounded by dark brown interlobular tissue. The liver substance is almost entirely taken up by irregularly rounded, soft, dark yellowish-white nodules measuring from 1 to 3 mm. These nodules are more numerous at and around the hilum, and they are in places small, light yellow and in others larger and almost diffluent, whitish yellow with many small white dots. On pressure one can squeeze out dark brown material mixed with light yellow and dark red substance. The hepatic veins and artery are found free from any suppuration, but the portal vein is blocked for a distance of about 10 cm. from its free course, with soft red material striped with yellow. As the vein enters the liver this material is so adherent to the wall that it seems as if it were growing from it. From this point on to the finest visible branch the vein is blocked with the same material.

The remaining organs correspond in appearance with the gross anatomical diagnosis: Carcinoma arising in liver, with extension into portal vein; thrombosis of pulmonary artery; ascites; chronic perisplenitis, slight splenic tumor; follicular cholecystitis; dilatation of common and cystic bile ducts and gall-bladder; congestion of lungs; arteriosclerosis.

Microscopically, several slides were studied and the report is a composite one. The outer capsule is considerably thickened and the perilobular connective tissue markedly increased. The interacinous bile-ducts are moderately increased in number but not so much so as would be expected for the grade of cirrhosis. The veins are much congested and in many cases filled with neoplastic thrombi. The cells of the parenchyma show advanced cloudy swelling and central atrophy, but the most striking change in them is a wide-spread necrosis which appears in both

peripheral and central positions and is too extensive to be looked upon as the usual expression of focal necrosis. The central veins are markedly congested but show little fibrosis. Throughout the lobules but most noticeable in their periphery are enormous numbers of amorphous dark green pigment masses, very clearly defining the intralobular bile capillaries in the unstained specimens. The tumor masses are distributed irregularly and profusely throughout the sections, often more or less limited to the perilobular structures, again penetrating clearly within the acini. The cells are of irregular outline and variable size but generally somewhat larger than the liver cells. They are arranged in clumps which are quite free from connective tissue (with Mallory stain) and show no attempt at gland formation. The protoplasm is rich and vacuolated as if by fat globules. The nuclei are large, oval, vesicular and show frequent mitoses. Here and there large protoplasmic masses are found containing multiple nuclei. In masses quite free from veins, fairly large areas of hemorrhage are found. No transitional connection between liver parenchyma and new growth can be demonstrated. The large number of neoplastic thrombi in the perilobular veins is a striking feature. Sometimes the thrombi appear to dilate the veins. In other cases the veins are not dilated very markedly but are completely occluded by the tumor cells. A few of these neoplastic masses are in perivascular situations and would seem to be lymph spaces rather than veins. In some of the larger veins much of the elastica has been destroyed by the tumor growth.

Microscopical examination of the other viscera was made and no metastases noted. Microscopical diagnosis: Carcinoma solidum of liver with extension into portal vein; passive congestion, necrosis, biliary pigmentation of liver; congestion and follicular hyperplasia of spleen; chronic diffuse nephritis.

To summarize, this is a case of primary carcinoma of liver of solid form, occurring in a Chinaman 56 years of age. Clinically there is a history of opium-smoking, short duration of illness, emaciation, jaundice, ascites and slight edema of feet and ankles. Pathologically there is the tumor with portal vein thrombosis, no metastasis, slight splenic tumor, and the thrombosis of the pulmonary artery which appears not to have been neoplastic. Hemorrhage is noted in tumor areas but is very slight. It is significant, however, in that in one case at least, that of Ewing,[12] it was severe enough to have been the cause of death.

CASE 7.—*History.*—L. F., an Italian, aged 34, was a patient in the Pennsylvania Hospital (1,152), on the service of Dr. Tyson. The records and specimens were furnished me by Dr. Longcope. An abstract of the history follows: Chief complaint, jaundice, abdominal pain and fulness. The family history is negative. The patient is a steady drinker, smokes to excess; good appetite; bowels regular.

Physical Examination.—Well nourished, skin quite yellow; skin of flanks scarred in linear striæ as if by distention. No marked prominence of abdominal veins. Tongue coated; teeth good. Thorax, lungs and heart negative. Abdomen tense, dome-like tympanitis in upper part, movable dulness in flanks. Spleen not palpable, no tension nor rigidity. Liver, sixth rib to costal margin.

Urine: cloudy, brown, 1.018, acid, faint trace of albumin, much bile, few hyaline and granular casts.

Blood: hemoglobin 87 per cent.; leukocytes, 11,300, of which 88 per cent. were polymorphonuclears; 3 per cent. small, and 4 per cent. large lymphocytes; 4 per cent. eosinophils; 1 per cent. basophils.

Jaundice increased, as did the emaciation. Patient developed constipation and anorexia.

12. Ewing: Proc. New York Path. Soc., 1906, new series, vi, 168.

Cytolytic examination of the fluid in the abdominal cavity showed many large mononuclear cells.

Necropsy.—This was performed by Dr. Longcope nine hours after death, whose notes are abstracted as follows: Liver measures 27 by 19 by 10 cm.; weighs 1,800 gm. It is of a deep green color and presents a rough, irregular, hobnailed appearance. In several places on the surface the hobnails stand out, being bright green or pale yellow in color. These yellow nodules are scattered and not numerous. On section the cut surface shows a coarse, bright green, irregular lobulation. Here and there the same grayish or pale yellow lobules take the place of the green lobules. Over one area about 5 cm. in diameter there are several raised, very sort bright yellow rounded nodules showing some centrally placed radiating red striæ. When cut they show soft pus-like centers in an irregular cavity. There are various openings in the cavity which can be traced directly into the main hepatic duct and when the puriform material is removed the wall of the cavity is found to be lined with a well-defined white membrane. At some distance from the central mass there are small soft raised yellow masses which connect directly with the main cavity. When the portal vein is opened it is found to be filled with a tumor-like mass about 5 cm. across. This is situated at a point where the vein divides and completely occludes and distends it. The mass is soft, friable, orange-yellow streaked with red and firmly adherent to the wall of the vein. It extends for some distance down the branch running to the left lobe where it becomes soft and of the same nature as the tumors filling the bile-ducts and cavity in the liver. The same condition is seen in the main portal vein, where the tumor gradually tapers down to a red clot which partially fills the vessel and does not extend as far as the entrance of the splenic and superior mesenteric veins. No connection can be found between the main branches of the portal vein and the bile-ducts or the large softened areas in the liver.

The other organs correspond in appearance with the gross anatomical diagnoses: Atrophic cirrhosis of liver; tumor arising at hilum and involving and occluding the portal vein and hepatic duct and its branches; splenic tumor; ascites (2,600 c.c.); subserous hemorrhages of stomach, intestines and pericardium; hemorrhage from mucous membrane of colon; general icterus; acute seropurulent pericarditis; congestion and partial atelectasis of lungs; congestion and jaundice of kidneys with chronic diffuse nephritis; chronic intestitial pancreatitis with fat necrosis.

Microscopically, several specimens of liver were examined, the notes making a composite picture. The outer capsule is fibrosed and the perilobular fibrous tissue is overgrown and richly infiltrated with lymphocytes and a few leukocytes. The blood-vessels are congested and several of the veins show neoplastic thrombi. The bile-ducts are enormously increased in number and appear both in interlobular and intralobular position. When in intralobular positions they are accompanied by an overgrown connective tissue mass, quite free from elastica. These ducts often show terminal clubbing, the cells in the clubbed area being identical in morphology with liver cells but not containing bile pigment. The liver lobules are irregular in outline and often much diminished in size. The cells of the parenchyma show well-marked cloudy swelling and in the center of the lobule are atrophic. The finer bile canaliculi are choked with amorphous dark green bile-pigment throughout. Many extensive areas of necrosed liver cells are observed. The tumor masses are scattered irregularly over the field and usually show as fairly well defined areas somewhat larger than a liver lobule made up of large irregular cells about the size of a liver cell and with identical tinctorial characters. The protoplasm in many shows fine vacuoles similar to the fat vacuoles of liver cells. Mitotic figures are not frequent and nuclear fragmentation is common. These areas show central necrosis and often are infiltrated rather richly with polymorphonuclear leukocytes. Extension into the veins is fairly common, in most cases the vessels being completely occluded and slightly distended by the solid tumor masses. In no place where the tumor is definitely malignant can any attempt at gland formation be made out. Invasion of the sheath of one of

the smaller nerve-trunks is observed but is not extensive. This is a feature that has been described as being prominent in a case reported by Conti.[4] No connection can be observed at any point between liver tissue and tumor or the proliferated bile-ducts and tumor. The growth in the portal vein is like the main tumor mass. The cells are attached to the wall of the vein, which latter is partly distended.

Other organs were examined microscopically, the diagnosis including: Carcinoma solidum, atrophic cirrhosis, necrosis, neoplastic thrombosis of liver; hemorrhages in pericardium, duodenum and gall-bladder; chronic interstitial pancreatitis with fat necrosis.

To summarize, this case is one occurring in a man 34 years of age. Clinically he has a history of alcoholism, shows emaciation, icterus and ascites. Pathologically the liver tumor appeared as if it might have started from the larger bile-ducts, but histologically it is a cancer whose cells so closely resemble those of the liver that they must be responsible for its origin. There is cirrhosis and venous thrombosis but no evidence of metastases outside the liver.

CASE 8.—*History.*—D. I., a Russian boy, aged 8, was a patient in the Pennsylvania Hospital (1,295), on the service of Dr. Mitchell. The specimens and records were furnished me by Dr. Longcope. A brief abstract of the clinical history follows: Chief complaint, abdominal pain. Patient's mother says the boy has been sick about a week but was taken acutely ill about two nights before admission with severe abdominal pain accompanied by vomiting and pain on the right side. He had also been having a cough with yellowish thick expectoration; headache, pain all over, fever for two days, loose stools, no chills, no convulsions.

Physical Examination.—Fairly well-nourished boy; tongue heavily coated. Lymph-nodes not palpable. Lungs show a few scattered bronchial râles. Heart, rapid, pulse weak, fairly loud systolic murmur heard best at apex. Abdomen distinctly tender in lower right quadrant, slightly rigid; no mass palpable. Extremities are negative. Examination of blood in receiving ward shows 35,000 leukocytes.

Operation was performed on admission after which the patient grew steadily weaker and died. Urine, after ether, acid, 1.010, trace of albumin, many granular and hyaline casts, epithelial cells, leukocytes.

Necropsy.—This was limited to the abdomen and was performed by Dr. Draper, whose notes are abstracted as follows: Liver, about normal in size, measures 18 by 12 by 6 cm.; is filled with nodular masses of varying sizes, the largest being half the size of a lemon. The capsule of the organ is smooth and glistening. Surface only slightly irregular. The color of the organ is purplish brown mottled with pale yellowish areas where the large masses shine through; these represent the sections of tumor masses. The liver tissue itself exists as narrow strand-like masses between the tumors. It is pale purple in color mottled with yellow. The markings are not recognizable. The tumors themselves are yellow, sharply defined and firmer than the liver tissue. They have a tendency to bulge above the cut surface.

The other viscera show congestion and there is splenic tumor and follicular hyperplasia. The gross diagnosis of the liver was multiple adenoma.

Microscopically several sections of the liver were studied. The outer capsule of the liver is moderately overgrown and the perilobular connective tissue also shows well-marked fibrosis. The blood-vessels are moderately congested and there is extensive neoplastic thrombosis of the perilobular veins. Increase in the number of bile-ducts between the acini is noted but is not very marked. The peripheral cells of the lobules show marked cloudy swelling; many of the central cells show well-marked vacuolation from the presence of fat. The nuclear changes

in the parenchyma are notable, there being enlargement and increase in the number of nucleoli in the peripheral cells, and diminution in size, fading and peripheral grouping of the chromatin in many of the central cells. The central vein is moderately congested. The larger tumor masses are surrounded by fairly dense connective tissue masses free from smooth muscle and very poorly supplied with elastica. The masses are solid peripherally and necrotic centrally, but show no areas of hemorrhage. The cells are large and irregular in outline, grouped in masses without fibrillar tissue. The protoplasm is often the seat of very well-marked vacuolation and a few multinucleated large protoplasmic masses are found. Mitotic figures are fairly numerous. The mass is not limited by its fibrous tissue capsule but pushes out in all directions, through veins and lymph-spaces, through perilobular and intralobular tissues. In the last situation fine cords of tumor cells are found in continuity with liver chains but no transitional connection is seen. The extension in the veins is well demonstrated with the Mallory connective tissue stain and by the Weigert elastica stain. There are also numerous solid finger-like tumor masses running through the interlobular connective tissues in well defined spaces free from muscle and blood which evidently are lymph-spaces.

Slides from other tissues were examined and the histological diagnosis includes: Carcinoma solidum, fatty degeneration, passive congestion, carcinomatous thrombosis of liver; congestion and cloudy swelling of kidneys; general lymphatic hyperplasia; slight post-mortem degeneration of adrenals.

To summarize, this case is one of primary carcinoma of the liver in a boy 8 years of age. Clinically there were indefinite gastro-intestinal symptoms, pain and tenderness over the liver, leukocytosis, absence of icterus and ascites. Pathologically the tumor is a carcinoma solidum, grossly of the type often called "multiple adenoma" associated with neoplastic thrombosis of veins but without metastases other than local, unless there were metastases in the unexamined lungs.

CASE 9.—*History.*—C. B., an Italian man, aged 40 years, was a patient in the Pennsylvania Hospital (304). The specimens and records were furnished me by Dr. Longcope. The patient was admitted in October, 1902, and his clinical history is abstracted as follows: Patient had severe attacks of chills and fever for eight days in the previous July and again in August two weeks later, when he became intensely jaundiced which continued up to the time of admission. During the past four weeks patient has had a dull aching in the hepatic region about the costal margin; no vomiting; stools clay-colored.

Examination.—On admission patient was intensely jaundiced. Liver extended 5 or 6 fingers' breadths below the costal margin, felt hard, smooth and regular. Gall-bladder was not palpable, the entire hepatic area vague in outline and patient had a constant dragging pain, relieved by lying on the right side.

Pain in hepatic area increased during the patient's stay in hospital. Gall-bladder was drained September 29, but patient died October 3.

Necropsy.—This was performed by Dr. Flexner, four hours after death. His notes at the time are abstracted as follows: Liver weighs 2,400 gm.; measures 21 by 21 by 13 cm. It is fairly large, and of exceedingly firm consistence; it is of a brilliant green color, mottled finely with irregular yellow and black markings. The surface is slightly irregular but not lobulated and smooth with the exception of a few fresh adhesions to the gall-bladder region. Near the lower margin of the right lobe there is a yellow depressed scar, irregular, but in general about 3 by 2 cm. in diameter. It lies about 1 cm. below the general surface and the margins are composed of liver tissue, rounded and contracted down to it. Six more such yellow depressed scars are found over the surface, varying from 0.5 to 2 cm. in diameter.

The gall-bladder is distended and shows a quantity of reddish, semi-liquid blood clot. The common bile-duct shows a most marked distention, measuring 4 cm. in diameter and 10 cm. in length; about it are several flattened soft large lymph-nodes; there is no constriction of the duct whatever. The distention of the duct extends into the liver and when the clots are removed a grumous fluid mixed with pus pours from the duct within the liver when the organ is pressed.

On section through the liver the surface has the same mottled grass-green and yellow aspect as the capsule. Lobular markings are obliterated. Near the hilum the bile-ducts are enormously distended and filled with dark grumous material and pus. In the middle of the right lobe a yellow irregular, opaque area is cut through similar to those on the surface, and in the left lobe another such area is found. Small yellow opaque discrete extensions radiate toward the surface of the liver, but toward the hilum these areas are covered with soft reddish-green necrotic mass. Connective tissue is much increased in the hilum and extends into the vessels and into the lobules of the organ.

Autopsy showed a small amount of fluid in the abdominal cavity and the various viscera corresponded in description with the gross anatomical diagnosis: Cirrhosis of liver with multiple adenomata; acute hemorrhagic cholangeitis; distention of common bile-duct but no cholecystitis; acute bronchopneumonia; chronic interstitial splenitis; chronic diffuse nephritis; general icterus.

The microscopical picture offered is a composite of several slides. The outer capsule is of about normal thickness and the perilobular fibrous tissue is considerably overgrown. The blood-vessels show well-marked congestion and several are distended by neoplastic thrombi, which will be described later. The interlobular bile-ducts are markedly increased in number, irregular in outline, often appearing as solid cords and with connective tissue appear to be replacing liver parenchyma. The liver cells show advanced cloudy swelling and toward the central vein distinct atrophy. The vein is moderately congested. All the sections show small necrotic areas, less extensive than a lobule, irregularly placed, sharply outlined and containing compound granule cells whose nuclei have disappeared, evidently necrotic liver-cells. Hemosiderin pigmentation and bile pigmentation of the liver cells are observed, the former especially in the neighborhood of the necrotic areas. In one slide an area 5 mm. in diameter is made up almost entirely of irregularly arranged fibrous tissue, rich in fibrillæ and poor in nuclei. An interesting feature of this mass is that, with the Weigert elastica stain, it is almost black. About its margin the number of small bile-ducts is very great. Several fairly large bile-ducts are included in the sections and these are filled with blood and the blood apparently has extended into the smaller ducts, for in the immediate neighborhood several small ducts whose morphology is typically that of the "proliferated" ducts there is also much blood. The tumor itself is of the solid type, showing as masses of epithelial cells irregularly grouped together in fairly large clumps surrounded by a connective tissue mass but distinctly infiltrating it. The cells vary from columnar and cuboidal cells to large irregular cells, and in some places large multinucleated protoplasmic masses are found. The cell nuclei are large, vesicular and generally oval in shape, and numerous mitoses are found. No connection with preexisting liver tissue is found. Several large veins are included in the sections. With the special stains they show a small amount of smooth muscle and several bands of elastica. They are almost filled with a thrombotic mass, which toward the vessel wall is solidly made up of cells like those found in the tumor masses, but which centrally becomes more and more mixed with clotted blood. The lumina are small but not completely occluded in any case. In spite of this extensive thrombosis no metastases were observed other than those seen in the liver itself.

Sections of other tissues were studied and the histologic diagnoses are: Chronic interstitial splenitis; chronic diffuse nephritis; carcinoma solidum, cirrhosis and focal necrosis of liver.

To summarize, this case appeared in a man, aged 40 years. Clinically the case was of short duration, showed icterus, slight ascites and pain

in the liver region. Pathologically the tumor was grossly of the type often called "multiple adenoma," showed local metastases, neoplastic thrombosis, cirrhosis, bile duct proliferation and focal necrosis.

In reference to the preceding two cases it must be said that the term multiple adenoma has a significance in connection with diseases of the liver that it does not have in other connections. Von Griesinger,[13] Rindfleisch[14] and Eberth[15] took the view that it is a distinct pathologic entity. Among the first to combat this view was Gilbert,[16] and of the more recent writers taking this position are Cloin,[17] Muir[18] and Alezais and Corsy.[19] Masterly, however, is the summing up by Marckwald,[20] who states in no uncertain terms that this tumor is a cancer. Further, he states that the more or less definite fibrous capsules around the tumor masses are made

TABLE OF NINE CASES OF PRIMARY

Case, Age and Sex	Nature of Cancer	Origin	Cirrhosis	Changes in the Liver	
				Cells	Bile-Ducts
1—40—F.	Adenocarcinoma of the massive form	Smaller bile-ducts	Present	Cuboidal and low columnar; mitoses common	Proliferated; interacinous
2—49—M	Adenocarcinoma of the nodular form	Smaller bile-ducts	Very slight	Low columnar; mitoses infrequent	Proliferated; interacinous
3—11—F.	Adenocarcinoma of the nodular form	Smaller bile-ducts	Present	Low columnar; no mitoses; necrosis	Proliferated; interacinous
4—53—M.	Adenocarcinoma of nodular form; shows solid masses also, histologically	Smaller bile-ducts	Marked	Low columnar; mitoses	Proliferated; interacinous
5—52—M	Adenocarcinoma of the nodular form	Smaller bile-ducts	Moderate	Low columnar, often showing transition to hepatic cell forms; numerous mitoses; necrosis	Proliferated; interacinous
6—56—M.	Carcinoma solidum of nodular form	Liver-cells	Moderate	Liver-cell type; frequent mitoses; necrosis	Slightly proliferated; interacinous
7—34—M.	Carcinoma solidum of nodular form	Liver-cells	Marked	Liver-cell type; infrequent mitoses; necrosis	Markedly proliferated; interacinous and intra-acinous
8—8—M.	Carcinoma solidum of nodular form, "multiple adenoma"	Liver-cells	Moderate	Liver-cell type; numerous mitoses	Slightly proliferated; interacinous
9—40—M	Carcinoma solidum of nodular form, "multiple adenoma"	Liver-cells	Moderate	Liver-cell type; numerous mitoses; focal necrosis	Markedly proliferated; interacinous

up for the most part of newly formed connective tissue, the course is relatively short and the condition may be the chief cause of death. Ribbert[21] offers a new class of somewhat similar tumors which he calls malignant adenomata of the liver, tumors originating in liver-cells, extending through the organ by continuity in the vessels or through metastasis by

13. Von Griesinger: Arch. f. Heilk., 1864, v, 385.
14. Rindfleisch: Arch. f. Heilk., 1864, v, 395.
15. Eberth: Virchows Arch. f. path. Anat., 1868, xliii, 1.
16. Dérignac et Gilbert: Gaz. méd. de Paris, 1884, lv, 28.
17. Cloin: Prag. méd. Wchnschr., 1901, xxvi, 261.
18. Muir: Jour. path. and Bacteriol., 1908, xii, 287.
19. Alezais and Corsy: Marseille Méd., 1908, xiv, 353.
20. Marckwald: Virchows Arch. f. path. Anat., 1896, cxliv, 29.
21. Ribbert: Deutsch. med. Wchnschr., 1909, xxx, 1607.

way of the portal vein and showing the power of bile-production. This is a tumor with functional powers simulating the function of the cells from which it originated.

Such classifications, however, can only serve to confuse a subject already complex and neither the malignant adenoma nor the multiple adenoma differ from the ordinary forms of liver cancers sufficiently to justify the separate classification. This point of view is taken by the majority of modern writers and my study of the subject leads me to accept it without further qualification. For this reason Cases 8 and 9 have been included in this series.

The accompanying table is modelled after Eggel's table and slightly modified. The cases are not sufficient in number to permit far-reaching

CARCINOMA OF THE LIVER

Blood-Vessels	Extra-Hepatic Metastases	Duration	Etiology	Jaundice	Ascites	Edema	Splenic Tumor
Slight tumor thrombosis	Right adrenal and subhepatic lymph-nodes	3 months	Coffee	Present	None	None	Present
Slight tumor thrombosis	Lungs, pleura, pancreas, left kidney, retroperitoneal lymph-nodes	1 week (?)	Lead	None	Moderate	(?)	None
No thrombosis	None	11 months	.....	Present	Marked	Marked (anasarca)	Marked
Moderate tumor thrombosis	Lungs, mediastinal, retroperitoneal and mesenteric lymph-nodes	2 months	Tobacco enough to produce leukoplakia	Slight	Present	Present	Present
Blood thrombosis not neoplastic	Pancreas, adrenal, peritoneum, mesentery, pleura, lymph-nodes	4 months	Alcohol	Present	Present	Present	(?)
Tumor thrombosis in portal vein	None	2 months	Opium (?)	Present	Present	Present	Slight
Tumor thrombosis	None	(?)	Alcohol	Present	Present	None	Present
Extensive tumor thrombosis	None (?)	1 week	.....	None	None	None	Present
Tumor thrombosis	None	4 months	(?)	Marked	Slight	None	None

conclusions to be drawn, but a brief analysis seems advisable. The age of the patient is altogether in late middle life with the exception of two cases which have appeared in rather early life. Philipp[22] states that cancers of the digestive tract, including liver and pancreas, contribute 46 per cent. of all cancers occurring before the age of 15 years. In Eggel's statistics there were but five cases occurring before 20 years of age. Cade,[23] Petrone,[24] Risicato,[25] Majumdar,[26] Mattirolo,[27] Wegelin[28]

22. Philipp: Ztschr. f. Krebsforsch., 1907, v, 236.
23. Cade: Lyon Méd., 1906, cvii, 1053.
24. Petrone: Pédiatrie prat., 1907, v, 109.
25. Risicato: Pediatria, Naples, 1905, series 2, iii, 772.
26. Majumdar: Indian Med. Gaz., 1905, xl, 306.
27. Mattirolo: Gaz. d. osp., 1905, xxvi, 732.
28. Wegelin: Virchows Arch. f. path. Anat., etc., 1905, clxxix, 95.

have reported cases in early life and it would appear that, as the study of carcinoma in early life is prosecuted further, cancers of the liver will be found to be of somewhat greater frequency than is supposed at the present time.

Little need be said as to sex, for the predominance of this affection in the male sex is well shown in the table (seven out of nine cases) and similar proportions are recorded by all modern writers.

The microscopic character of the tumor is found to be adenomatous in five cases and simple or solid in four cases. Various writers disagree as to which form predominates and Eggel's statistics show the reversed proportion, sixty-two cases of carcinoma solidum and fifty-five cases of carcinoma adenomatosum. That statistics might be very much prejudiced is well shown by the fact that all my own cases were of the type of adenocarcinoma and of the five cases furnished me by Dr. Longcope four were of the solid type. Grossly eight of the nine cases are nodular cancers, the other being a massive type. The predominance of the nodular form is more marked in my series than in series of greater number, and all statistics point to this as the most frequent form. The diffuse cancer is one which resembles a hypertrophic cirrhosis so closely in the gross that it is often impossible to make the diagnosis without the microscope.[29] It is a rather rare form, constituting about 12.4 per cent. of the reported cases.

The cells from which the tumor originated have been put in the table with some mental reservation, for, although some authors have reported seeing transformations directly from liver-cells into cancer, and from bile-ducts into cancer a detailed study of these nine cases fails to convince me that such transformation can be demonstrated. A very close resemblance can be seen between the tumor-cells in some of the cases and liver cells as is true also of the duct epithelium and the tumor-cells; but inasmuch as transformation of the morphology of the cells can be seen very distinctly in the small bile-ducts in cirrhosis of the liver and in regeneration after acute processes such as acute yellow atrophy,[30] it would seem reasonable to suppose that such transformation can occur in neoplastic processes, thus interfering with deductions drawn on a purely morphological basis.

The question of the association of cirrhosis and cancer of the liver is a living one and is the basis for a wide range of discussion and opinion. It will be noticed that all nine cases show more or less marked cirrhosis. Of Eggel's cases cirrhosis was mentioned clinically in connection with eighty-two and found present at autopsy in seventy, the proportion being about the same in the two microscopic forms.

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29. Herzheimer: Centralbl. f. allg. Path. u. path. Anat., 1906, xvii, 724.

30. Mac Callum: Johns Hopkins Hosp. Rep., 1902, x, 375. Barbacci: Beitr. z. path. Anat. u. z. allg. Path., 1901, xxx, 49.

Two essential views are held as to this relationship, the first being that the two are present in the livers simply as the result of coincidence, Frohmann[31] taking this stand. It is true that relatively few cases of cirrhosis of the liver show cancer, yet they show cancer-like changes in the increased number of ducts and the isolated islands of irregularly arranged liver-cells, sometimes, in my experience, to such a degree as to render the final diagnosis very difficult. Rolleston[32] goes so far as to say that mistakes of this sort have been made in many cases. In spite of this, the very marked frequence of their concurrence, and the fact that secondary cancers are not very commonly associated would lead me to reject such a view.

By those who believe that the two conditions are more or less interrelated, several views are expressed. Gilbert and Claude[33] with some others assert that the cancer is the primary process and produces the cirrhosis, probably by producing stagnation of the bile or by the direct action on the connective tissue of the toxic products of the cancer itself. Bile-stagnation, however, although common, does not appear in all cases and, as has been mentioned before, the occurrence of secondary cancers frequently is unassociated with cirrhosis. The weight of opinion is decidedly against this view.

Many claim that the cirrhosis precedes the cancer and is etiologically at the basis of the malignant growth. To appreciate this view it is necessary to accept the view that cirrhosis is secondary in itself to some injury to liver substance and that the fibrosis occurs as a replacement process. Clinical and experimental observation point this way so strongly that the assumption seems fully warranted. Following out this idea leads us far afield into the study of liver regeneration, a study probably first undertaken from the experimental side by von Podwyssowski.[34] He found that in different animals the removal of fairly large pieces of liver were followed by proliferative changes in the connective tissue and epithelium, the latter in some animals being more marked in the finer bile ducts and in other animals in the liver cells. Ponfick[35] reached somewhat similar conclusions. Of the more recent experiments those of Jaeger,[36] studying aspergillus mycosis in deer, led him to express the same view. Many workers in human pathology are of the opinion that bile-duct proliferation *or* multiplication of the hepatic cells occurs as the sole means of regeneration but personal observation of several hundred degenerate livers, including many cases of cirrhosis, leads me to accept the view that both liver cells *and* bile-ducts play a part in liver regeneration and that

31. Frohmann: Inaug. Diss., Königsberg, 1892.
32. Rolleston: Tr. Path. Soc., London, 1901, lii, 203.
33. Gilbert and Claude: Arch. gén. de méd., 1895, clxxv, 513.
34. Podwyssowski: Beitr. z. path. Anat. u. z. allg. Path., 1886, i, 259.
35. Ponfick: Virchows Arch. f. path. Anat., 1895, cxxxviii, 51.
36. Jaeger: Virchows Arch. f. path. Anat., 1909, cxcvii, 45.

the connective tissue overgrowth is essentially a substitution process. This view is supported by Mac Callum[37] and others who have made extensive studies in this field. The multiplication of liver-cells according to my own observation is almost certainly by amitotic division, but I am not prepared to state the mode of division into the multiplication of the bile-duct epithelium.

That diffuse or more or less localized destruction of the liver parenchyma may lead to very marked proliferation of both interstitial and parenchymatous elements has been referred to earlier. In order to apply this fact to cancer production it is necessary to call on Orth's view, expressed in his "Lehrbuch," that the epithelial proliferation overshoots the mark and produces malignant change. That necrosis or other degenerative change might have played a part is suggested, but not proved by any means, by the fact that in my series four cases showed it extensively and that in Case 9 a focalized scar was found, probably the result of an earlier focalized lesion.

The frequent proliferation of bile-ducts is called on to support the view that cirrhosis is primary, but I cannot accept this because I find it present equally in the cases of liver-cell cancer as well as in the adenocarcinomata, and in no case was I able to find connection between the proliferated bile-ducts and the cancer. This phase of the subject will be referred to later.

Fraser[38] in this connection suggests the ingenious explanation that there is present in the first place a hypertrophy of the connective tissue which first is loose, later shrinks irregularly and causes on the one hand a destruction of parenchyma, on the other hand compensatory proliferation, particularly in the parts not shrunken or in such places as there is little resistance to overcome. The balance of proof certainly lies with Fraser, as this supposition is in marked contrast to the generally accepted ideas as to the pathogenesis of cirrhosis.

A third view as to the relation of cirrhosis and cancer is that a productive or organogenic irritant produces proliferation of connective tissue, bile-ducts and liver parenchyma. This view is ably supported by Jaeger[36] in his work on deers' livers. There are many considerations which force me to regard this view favorably and numerous writers take the same position, but again we are carried too far afield to warrant discussion in this paper.

The presence of tumor thrombosis is of very great interest in explaining metastasis, ascites and splenic tumor. That metastasis is not more frequent in connection with thrombosis is probably due to the rapid

37. Mac Callum, W. G.: Regenerative Changes in Cirrhosis of the Liver, Jour. Am. Med. Assn., 1904, xliii, 649.

38. Fraser: Virchows Arch. f. path. Anat., 1901, clxv, 540.

growth of the cancer and in few of these cases was there necrosis in the thrombi, a feature which means little probability of embolism.

Metastasis in the liver is a common feature, as can be readily explained by the rich blood-supply and the numerous lymph-vessels which course through the trabeculæ. Extrahepatic metastases are most common in the lung, although my series of cases does not give very much information as to this point. This feature, however, is almost certainly due to the rich venous thrombosis which occurs in connection with so many of these tumors. In spite of this fact, fairly rich thrombosis is found in cases where no extrahepatic metastases are recorded whatever, and as has been stated above, this can be due to the rapid growth of the tumor and the fact that necrosis is very infrequent in the thrombi.

The duration of the disease is short in all cases, another point borne out by all the statisticians. Two of my patients give a history of having been ill but a week. Naturally this cannot be accepted as final because of the notable inaccuracies of histories, particularly in the class of patients seen in the hospitals from which these cases were taken. Nevertheless that liver cancers run a course more rapid than cancers of most other viscera is a well-supported fact and is explained probably by the fact that the toxic products of the cancer have unusually ready access to the circulation, as can be inferred from the frequent venous thromboses. Again, metabolic and digestive functions of the liver are of extreme importance and the fact that the tumor spreads rapidly through the liver by virtue of the intercommunicating blood and lymph-spaces would lead to very rapid interference with these functions.

As to the history of the use of drugs which would lead to cirrhosis I have included coffee and opium and tobacco, which although not generally accepted as causes of cirrhosis, most certainly play an important part in its production. This point being accepted, all our cases with the exception of the two children and the last case show a history which includes some etiologic factor in the production of cirrhosis. This point should be regarded with considerable interest in connection with the question as to whether cirrhosis or cancer is primary.

Jaundice was present in seven of my nine cases and Eggel found it in 61 per cent. of his cases. The histologic character plays little part statistically in the presence or absence of jaundice although grossly the condition is less frequent in the massive form than in the nodular form. Jaundice can be explained in various ways, probably most easily by assuming that the intrahepatic masses act to obstruct the outflow of bile. In Case 1 there was little doubt at the time of the autopsy that involved lymph-nodes in the hilum of the liver produced pressure on the hepatic duct and it is easily conceivable that such pressure might be sufficient to play an important part in the production of the icterus. The same is true of Case 5. Furthermore, the cachexia incident to liver cancers as

well as to other forms of cancer may be of moment in that the production of a cachectic anemia may lead to consequent hematogenous jaundice. Metabolic disturbances may add to this and there can be little doubt that the toxic products of altered metabolism may produce the so-called toxic jaundice.

Ascites was present in seven of my cases but not in precisely the same group which showed icterus. Eggel found it in 58.5 per cent. about equally divided between the massive and nodular forms and most frequent in the diffuse (hypertrophic cirrhotic) form. Curiously, it is more frequent in those cancers which show the liver-cell type histologically than in those of the gall-duct type. Although toxic factors and the presence of anemia may play some part in the production of ascites yet the most probable causes, I think, are the associated atrophic cirrhosis and the frequent venous thrombosis of neoplastic and other origin.

Edema of the lower extremities was present in four of my cases and probably in a fifth case. Eggel found it in 41 per cent. of his cases. In the majority of cases the edema must be laid to the anemia and toxemia but in a few it can be accounted for by the pressure of metastases, particularly those invading the lymph-nodes of the hilum, on the vena cava. Neoplastic or other forms of thrombosis in the vena cava have been known to produce edema in cases of cancer of the liver.

Splenic tumor is an inconstant feature in the larger series of cases but in my series it is seen to occur in six cases. The diagnosis in these cases is made from the point of view of the gross morbid anatomist and whether or not the clinician could demonstrate the condition in all these cases is, I think, questionable. It may be that toxic factors play a considerable part in the splenic enlargement and there can be little doubt that the general abdominal stasis is of great etiologic importance.

SUMMARY

To summarize, it may be said from the studies presented in conjunction with the literature reviewed, that primary carcinoma of the liver occurs more frequently in men than in women, is seen most frequently in the fourth and fifth decades of life and very often is accompanied by a personal history in which some etiological factor of cirrhosis of the liver is found. Clinically vague gastro-intestinal symptoms like those of early atrophic cirrhosis are noted and are followed by more marked digestive disturbance, cachexia and frequently jaundice. Ascites, edema of the lower extremities, splenic tumor and more rarely fever present themselves in a variable number of cases. The course of the disease is rapid.

Pathologically the disease shows three gross anatomical forms, nodular, massive, diffuse, and two microscopical forms, carcinoma solidum and carcinoma adenomatosum. In the liver itself cirrhosis is an associated condition in almost all cases, tumor thrombosis of the intrahepatic blood-

vessels is common and intrahepatic metastases are frequent. Extrahepatic metastases are more common and more widely spread than usually is believed and their distribution, together with the frequent presence of tumor thrombosis of the intrahepatic blood-vessels, lead to the conclusion that the transmission of the condition to the other organs is largely through the blood vascular system. In my opinion cirrhosis of the liver, or the factors which commonly are believed to produce cirrhosis, play an important part in the etiology of primary carcinoma of the organ and the tumor may originate from either the essential hepatic cells or from the bile-duct epithelium. These tumors arising from the liver-cells are more likely to be of the solid form and those from the bile-ducts are more likely to be of the glandular form, but this is not an invariable rule.

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BOOK REVIEWS

DISEASES OF THE HEART AND AORTA. By Arthur D. Hirschfelder, M.D., Associate in Medicine, Johns Hopkins University. With an Introductory Note by Lewellys F. Barker, M.D., Professor of Medicine, Johns Hopkins University. Cloth. Price, $6. Pp. 632, with 329 illustrations. Philadelphia: J. B. Lippincott Company, 1910.

It is almost as agreeable, and indeed quite as stimulating, to find an old subject presented in a new and suggestive manner as to chance upon a new subject itself, and the former, as a rule, is far more apt to be quickly and widely received. The tremendous strides which have recently been made in assisting us to understand the complicated mechanism of the cardiovascular apparatus, both in health and in disease, have developed a new and much broader point of view regarding heart disease. Until the publication of this book most of the contributions which have brought about this somewhat different attitude of mind had not been incorporated in the older text-books on the heart or modern system articles, nor have they exerted their full influence on them. The great value of the present book is that the author treats the subject in a new way. The recent results of anatomical, physiological, pathological and clinical studies are combined in such a manner that the direct bearing which the scientific observation or experiment has on the bedside teaching is most judiciously and carefully pointed out, and the results of recent investigations are used to make clear the fundamental changes which take place in disease.

The first part of the book is devoted to general considerations and methods of diagnosis, in which among others there are excellent chapters on the blood-pressure, the arterial and venous pulse and the electrocardiogram. In the second part "Diseased Conditions Due to Diffuse Pathological Processes" are discussed. In this section there are several chapters on cardiac overstrain, broken compensation and general symptoms of cardiac disease; excellent chapters on the general principles of treatment, the effect of drugs, gymnastics and hydrotherapy in cardiac diseases, and sections on the affections of the myocardium and the broad subject of arteriosclerosis with its results.

In the third part, the diseases of the various heart valves are treated separately, and chapters are devoted to heart block and Adams-Stokes syndrome, pericarditis, wounds of the heart and aneurysm. Finally, the book closes with chapters on "Functional Diseases Without Anatomical Lesions." Each chapter is introduced with a thorough discussion of the pathological physiology of the subject. As is inevitable in a book that deals with a subject to which knowledge is still being added, one finds statements which by this time would undoubtedly be modified by the author. The paragraphs on perpetual irregularity of the heart were evidently written before the recent work had shown conclusively that this condition was due in most cases to fibrillation and not paralysis of the auricles. So, too, in the section on arteriosclerosis, the author's views as to the etiology and classification of the diseases of the blood vessels are in places not as definite as one might wish, especially as regards the syphilitic type of mesarteritis. One very excellent feature is the great number of illustrations and diagrams which help immensely to present complicated problems in an objective manner. Most of these, too, are original and afford a great relief from the hackneyed cuts so common in most text-books. A selected bibliography is appended to each chapter. The monograph can be highly recommended to both students and practitioners, and whoever reads it will be sure to experience pleasure and gain much information.

A Treatise on Diagnostic Methods of Examination. By Dr. Hermann Sahli, Director of the Medical Clinic, University of Bern. Edited, with Additions, by Nathaniel Bowditch Potter, M.D., Assistant Professor of Clinical Medicine at Columbia University (College of Physicians and Surgeons), New York. Second Edition. Authorized Translation from the Fifth Revised and Enlarged German Edition. Cloth. Price, $6.50 net. Pp. 1229, with 471 illustrations. Philadelphia: W. B. Saunders Company, 1911.

Perhaps there is no single book on diagnostic methods which has had as wide influence as this treatise of Professor Sahli, and when we come to look for the reason, it is undoubtedly to be found in the fact that the treatise is not a mere description of methods of clinical examination, compiled from text-books and journal articles, but really a critical survey of the clinical procedures, almost all of which have been used and carefully tested in the clinic at Bern. It therefore represents actually the work of one man, and the stamp of his authority gives the book a value which it could attain in no other way. In many instances, moreover, the paragraphs on the use and value of certain instruments and methods of examination have appeared first in this book and, in a way, therefore, the treatise must be considered as an original communication. The fifth German edition has been very thoroughly revised and considerably enlarged. The chapter on hemodynamics has been entirely rewritten, and extensive revision has been made in practically every chapter in the book. These changes are particularly noticeable in the section on the examination of the stomach, the chapter on the blood, and the examination of the intestinal canal; but it is impossible here to mention in detail the various and numerous changes and additions. The American edition has been increased in size by over 200 pages, and yet some of the material in the last edition has been omitted or replaced by new matter.

In the chapter on physical diagnosis, the author describes at some length the value of the newer methods of percussion, such as the orthopercussion of Goldscheider, but rather advises against their use. There is no mention made of the third heart sound. Though the section on hemodynamics has been rewritten, and most of the modern methods of examination are critically surveyed, one is greatly astonished not to see a single word concerning the electrocardiograph; the instrument is not even mentioned. Several pages are devoted to sphygmobolometry. In the chapter on the examination of the stomach, there is a long description of the desmoid reaction, and the butyrometric method of the examination of the stomach contents is described much more fully than in the last edition.

In the chapter on the blood, very free use is made of Naegeli's *Blut-Krankheiten*, and most of his views on the origin of the blood-cells and the classification of diseases of the hematopoietic tissues are accepted. Considerable space, perhaps proportionately too much, is devoted to a discussion of the viscosity of the blood. The valuable chapter on the nervous system has been considerably altered and enlarged. Great credit is due to the translater and editor, for certain little inaccuracies and faults which were present in the first American edition have been corrected, and the present volume has been edited with much care and discretion. Comparatively few additions have been made, and these have been chosen most happily and almost all from the American literature. Chief among them are a note on Grocco's sign, a very useful paragraph on the collection of urine, Folin's method for the determination of acetone and acetoacetic acid, Schaffer's method for the determination of beta-oxybutyric acid, methods for enumerating platelets and Noguchi's modification of the Wassermann reaction and the butyric acid test for globulins in the spinal fluid.

A curious reduplication, however, has occurred in one instance, for Folin and Schaffer's methods are described on page 603 and again almost in the same words on page 656. It may be said that the present edition is almost like a new book, so greatly has it been changed and added to, and it is now unquestionably one of the most valuable treatises on diagnostic methods which we possess.

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PATHOLOGICAL ANATOMY OF EXOPHTHALMIC GOITER

THE ANATOMICAL AND PHYSIOLOGICAL RELATIONS OF THE THYROID GLAND TO THE DISEASE; THE TREATMENT *

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1. INTRODUCTION

The sixty-nine cases used as the basis of this report include all cases clinically diagnosed as exophthalmic goiter at Lakeside Hospital from Sept. 7, 1907, to Sept. 7, 1910, from which sufficient thyroid gland tissue was obtained for anatomical studies and for iodin determinations.

The principal data appertaining to each case have been tabulated as briefly as possible (Table 3). It will be noticed that special stress is laid on the objective phenomena obtained during the patient's stay in the hospital. This was done (1) because we have as yet no accurate standard of estimating the importance of subjective sensations in this disease, although they are doubtless of great importance in all nervous and mental diseases, and (2) because our major interest at present is concerned with the physiological relation of the thyroid gland to the symptom-complex.

2. PATHOLOGICAL ANATOMY

In describing the pathological anatomy of exophthalmic goiter we must be content at present with cataloging the changes in the various tissues of the body, in the order of their constancy and prominence. This amounts to describing the structural alterations of those tissues which biologically are endowed with the greatest means of physiological adaptability, and must necessarily leave uncharted much that may be of the greatest significance in tissues whose powers of objective manifestation of reaction are most limited. Thus it cannot be stated that, because the structural changes in the brain appear less marked than those of the lymphoid or thyroid tissues, therefore they are of less importance.

The morbid anatomy comprises changes in many organs. Indeed all the body tissues may be affected, as might be expected in a disease in which nutrition is so gravely impaired. It is on account of the attempts

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to raise the anatomical changes of certain tissues (formerly the nervous tissues, now the thyroid gland) to the rôles of primary factors that conflicting hypotheses and controversies have arisen.

We are not justified in ascribing a greater or lesser degree of importance to the anatomical changes than the experimental data of morbid physiology and of morbid chemistry make possible, for, in this disease, which is probably a general nutritional disturbance, it is by these means that the primary or causal alterations can be separated from the secondary or resulting alterations.

I. Thyroid Gland[1]

Widely different views are held concerning the character of the thyroid changes. There are those who hold that the changes are constant and specific. Others hold that the thyroid changes are neither constant nor specific; while still others believe that these changes are relatively constant but in no sense specific. These differences of opinion have arisen largely from the fact that (1) many writers have used very small series of cases as the basis of their conclusions, and (2) that great differences exist depending on whether the districts in which the cases arise are goitrous or not. Thus, in the cases arising in non-goitrous districts a single anatomical type of goiter (the small, generally symmetrical gland of from 40 to 150 gm. weight with uniform generalized fibrosis and active hyperplasia) predominates, while in cases arising in goitrous districts, as in the Alpine districts of Austria, Italy, Switzerland and France or in the Great Lakes Basin of America, a great variety of changes are met with, e. g., nodular (adenomatous) goiters, large, hemorrhagic-cystic goiters with extensive degenerative changes and large, simple colloid goiters, as well as the first form mentioned.

We have discarded four cases of clinically diagnosed exophthalmic goiter in which the anatomical changes in the thyroid were varied and highly complicated, in order to simplify the detection and interpretation of any relation of the idoin content to the histological structure and of any relation both of the iodin content and histological structure to the disease as a whole.

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1. Our studies have led us to the conclusion that the thyroid and parathyroid glands are independent structures both anatomically and physiologically. We have examined the parathyroids from nineteen patients with exophthalmic goiter, with findings similar to those reported by MacCallum, Med. News, N. Y., 1903, p. 820, viz.: That there is no anatomical or physiological evidence of any relation between the parathyroid and the exophthalmic goiter symptom-complex. Recently Roussy and Clunet (Compt. rend. Soc. de biol., 1910, lxviii, 818) have reported examinations of the thyroid-parathyroid apparatus in two congenital cretins who died at the ages of 25 and 28 years. They found that the lower parathyroids were normal in both patients while the upper pair was not detected in either. The thyroid lobes were extremely atrophic in one patient and absent in the other.

The thyroids of the sixty-nine cases used in this study (Table 3) are grouped as follows: (1) Normal thyroids (i. e., as regards gross appearance, histological structure and iodin content)—two cases. (1a) Normal-colloids (that is, glands in which one could not decide from their gross appearance, their histological structure or their iodin content whether they had or had not at some previous time undergone slight hypertrophy)—three cases. (2) Actively hyperplastic thyroids (i. e., including all the degrees of active hyperplasia from the slightest departure from the normal or the colloid gland to extreme cellular proliferation, whether occurring on a colloid or a normal thyroid basis)—forty-three cases. (2a) Premature atrophy supervening in active hyperplasia—four cases (included under hyperplasias). (3) Colloid goiters (pure type)—eighteen cases. (4) Fetal or simple adenomata (pure type)—eight cases (three included with normal-colloids and two with colloids). Thus, five of the nine[2] great divisions of the thyroid changes are represented. These five anatomical groups embrace all the known variations in the functional activity of the gland with which structural changes have been associated. We have grouped these changes in the following scheme in order to bring out their sequential relations and to render the following descriptions more easily understood:

1. Normal thyroids.
2. Hyperplasias:
    - I. Primary, i. e. developing on a normal gland basis.
        - A. Developmental stage.
        - B. Involuntary stage.
        - C. Atrophic stage.
    - II. Secondary, i. e. developing on a colloid gland basis.
        - A. Developmental stage.
        - B. Involutional stage.
        - C. Atrophic stage.
3. Colloid glands.
4. Adenomata.
    - I. Simple.
    - II. Fetal.
5. Old complicated goiters.

1. NORMAL GLANDS AND NORMAL-COLLOID GLANDS (SEE FIG. 1.)

The clinical diagnosis in the two cases with normal thyroids (using the most rigid standards) and the three cases with normal-colloid thyroids (ordinarily called normal) may be questioned, since goiter (anatomical standard) was absent in all five and exophthalmos in three. Such cases are not unique, however. MacCallum[3] records such an instance.

2. Marine and Lenhart: Pathological Anatomy of the Thyroid Gland, THE ARCHIVES INT. MED., 1911, vii, 506.

3. MacCallum: The Pathology of Exophthalmic Goiter, Jour. Am. Med. Assn., 1907, xlix, 1158.

Halsted[4] and others have remarked on the occurrence of the syndrome in individuals with normal glands. Such cases are ordinarily classed clinically as incomplete (*forme fruste*) exophthalmic goiter. They are more common than the literature indicates. Two possible explanations may be offered for such cases: either (1) thyroid hyperplasia was prevented by the presence of a high iodin content (a well-established fact for animals) or (2) the cases were not true exophthalmic goiter but some closely allied nervous symptom-complex, as neurasthenia or psychasthenia. Full descriptions of the anatomically normal gland have already appeared[5] and need not be repeated here.

2. ACTIVE HYPERPLASIAS (SEE FIG. 2)

In forty-three cases some degree of active thyroid hyperplasia was present. The degree of hyperplasia varied from the slightest departure from normal (hypertrophy) to the marked proliferations (hyperplasia). For reasons that have been discussed in previous papers, it is necessary to divide the hyperplasias into two groups, depending on whether they develop on the basis of normal (primary) or of colloid (secondary) glands. Clinically, this division of the cases into "primary" and "secondary" exophthalmic goiter has long been used. In presenting the anatomical characteristics of thyroid hyperplasia as they are observed in exophthalmic goiter one must bear in mind that the simplest conception includes parts of three different anatomical processes and of the three corresponding functional stages, viz.: (1) the developing of compensatory or hyperactive stage, (2) the involutionary or recovery or colloidal stage, and (3) the thyroid exhaustion or premature atrophy or myxedematous stage. All these stages overlap, both as to their anatomical and their physiological characteristics, so that in a given gland one may have any degree of one or more of the above named processes represented. It is preferable, therefore, to describe these stages separately, although *in vivo* such a separation does not frequently exist.

I. PRIMARY HYPERPLASIA

In a majority of the cases of exophthalmic goiter occurring in nongoitrous regions and to a much less extent in those occurring in goitrous districts, the hyperplasia develops from a normal gland base. We have grouped seventeen glands in this class. It might be designated as the classical type and, since the studies based on the surgical collections have so emphasized this change to the exclusion of others, a widely held opinion has been created that the thyroid changes in exophthalmic goiter are specific.

4. Halsted: Bull. Johns Hopkins Hosp., 1905, xvi, 288.

5. Marine and Lenhart: Relation of Iodin to the Structure of Human Thyroids, THE ARCHIVES INT. MED., 1909, iv, 440; 1911, vii, 506.

A. The Developmental Stage

Tracing the development of hypertrophy and hyperplasia from the normal gland, the first change noticed is the increased blood-supply. The capsular vessels, both veins and arteries, are dilated and hypertrophied. The capillaries surrounding the follicles are dilated. The gland becomes larger, softer, and takes on a brighter red color. Microscopically, there is a lessening of the stainable colloid. At first it merely stains less intensely; later vacuolization and finally a disappearance of the true colloid occurs, its place being taken by a granular albuminous débris in which may be seen leukocytes and shed epithelial cells. As the colloid disappears, the epithelial cells change from the normal cuboidal to high cuboidal, to columnar, and finally to high columnar, while preserving their uniformity and regularity. With the disappearance of the colloid and the growth in size and number of the epithelial cells, the color of the gland changes from the normal amber-red to reddish translucency, to gray-red, and finally to the soft, fleshy, gray-red and opaque color of the marked hyperplasia. As true hyperplasia of the epithelial cells takes place, the existing follicles enlarge and new ones are formed, probably by budding. Infoldings and plications begin to appear and may progress so as to almost fill the space originally occupied by the colloid. This infolding of the lining epithelium is largely dependent on the capsular and stroma tension. The gland capsule and stroma hypertrophy parallel with the epithelial proliferation. In the early stages of hyperplasia, this connective tissue-hyperplasia is relatively slight, while in the later stages the interlobular bands are relatively prominent and give to the gland a mildly hobnailed appearance. Complications, as hemorrhage, cyst formation, calcification, etc., are exceedingly rare. The entire gland shares these changes. The gland is symmetrically enlarged and preserves the outlines of its original or normal state. The enlargement is, of course, variable with the degree of active hyperplasia but rarely exceeds 200 gm. and, as we shall point out later, becomes smaller as fibrosis and atrophy supervene. The foci or nests of lymphoid tissue which develop in the gland stroma will be discussed under "Lymphoid Tissue."

B. Involutionary, Recovery or Colloidal Stage

The thyroid undergoes exceedingly rapid histological changes, both within the limits of health and of disease. These changes are for the most part of two types: (1) the developing hyperplasia, just described, and (2) its involution to the colloid state. These two processes of increased and decreased thyroid activity may alternate even from week to week, depending on different nutritional states of the body. They occur in all true goiters, in all animals, but are most pronounced in man on account of the more changeable conditions of nutrition and environment. In

exophthalmic goiter, owing to its spontaneous exacerbations and remissions, or to the treatment instituted, a progressive active hyperplasia of the thyroid is rarely allowed to continue its course undisturbed for a long time. Under such conditions the active hyperplasia ceases and may remain stationary, or it may partially involute to the colloid state, then undergo hyperplasia again, or the involution may be complete, in which case the gland returns to the pure colloid or resting stage. This in turn may be temporary or permanent, depending on the increased or decreased needs of the organism for thyroid activity. This involution, or return to the colloid state, occurs in all spontaneously recovering exophthalmic goiters (and in all other goiters as well) and invariably occurs following the administration of iodin-containing substances. It becomes obvious, therefore, that any given gland at the time of removal may be undergoing either progressive (actively hyperplastic) or regressive (involutionary) changes.

One must reckon with all degrees of this regressive or involutionary change from the marked hyperplasia back to the pure colloid gland, just as one has to reckon with all degrees of the progressive (actively hyperplastic) change from the normal or colloid gland up to marked hyperplasias. The anatomical changes are, therefore, just the reverse of those described under "developing hyperplasia" and are briefly as follows: The gland as a whole becomes firmer to the touch. The color changes from gray-red and opaque of the marked hyperplasias to gray-red and translucent, to reddish translucency and finally to the translucent amber-red color of the pure colloid gland. The blood-supply diminishes. This is associated with a lessening of the caliber of both the arteries and veins, due to a thickening of the vessel-walls similar to that observed in the involuting thymus or uterus. The follicles gradually become visible to the naked eye. They appear as enlarged, rounded cavities containing colloid—the latter at first but palely staining and granular, gradually becomes more uniform, more dense, stains more intensely and finally comes to resemble in all respects normal colloid. As the colloid accumulates the high columnar epithelium with its infoldings slowly returns to columnar, to cuboidal and finally to flat cuboidal, if the involution is complete, while the infoldings take on more of the appearance of small tufts of stroma jutting into the follicular lumen and covered with the prevailing type of follicular epithelium. Even the stroma becomes less prominent either by compression or absorption, and in the pure colloid state may show hyaline transformation. As a rule, this series of changes produces some lessening of the size of the gland as a whole. This, however, is a manifestation of minor importance.

These regressive changes may be prolonged for months or years or they may occur in a few weeks, depending on the degree of active hyperplasia existing at the time the involutionary process was instituted and

on the agents or factors underlying and producing the involution. All these changes may occur without altering the symptom-complex in any way. As a rule, however, there is some slight amelioration of the symptoms.

The question naturally arises how to distinguish and classify, anatomically, these regressive changes since, if they are the reverse of the progressive changes, corresponding degrees of either must have many anatomical features in common. They have. One may not be able to distinguish them. The iodin content is a material help, since it is usually lower in the developing hyperplasia and higher in the involutionary stage. Then a carefully taken clinical history may be of value. The greatest difficulty comes in separating these regressive changes from progressive changes occurring on a colloid base. Again the iodin content and a carefully taken history are the best aids. As regards classification, we have used the prefix "colloid" in conjunction with the degree of hyperplasia as, e. g., "colloid-moderate hyperplasia," since the process of involution necessarily implies the colloid phase.

C. The Exhaustion or Premature Atrophy or Myxedematous Stage

The thyroid cells in active hyperplasia are hyperactive. If this hyperactivity is allowed to continue without periods of physiological cell-rest, the cells sooner or later die of exhaustion. While this mode of termination of an active hyperplasia may occur in any clinical form of goiter in any animal, in the adult human subject it is most commonly seen in the end stage of exophthalmic goiter (myxedema) and in children, in the developing cretin. Clinically, the gradual replacement of the symptoms of exophthalmic goiter by those of myxedema has long been known, but its constant association with definite anatomical changes has not been specifically emphasized beyond the well-known clinical fact that in the late stages of exophthalmic goiter, the gland often becomes smaller and firmer. Anatomically the evidence of cell exhaustion and cell death in exophthalmic goiter is detectable before there is any clinical suspicion of a diminution of the functional activity of the gland. MacCallum[3] has clearly described these very early histological changes but did not point out their possible significance.

Just as one has to reckon with all degrees of "developing hyperplasia" from the normal gland up to the markedly hyperplastic stage, and with all degrees of the "involutionary or recovery stage" from the markedly hyperplastic gland back to the colloid gland, so in premature atrophy one has to reckon with all degrees of the process from the slightest atypical cell-growth in the markedly hyperplastic gland back to the small, scar-like thyroid in which are scattered islands of compressed epithelial cells.

Tracing the process from its first manifestations in a marked, active hyperplasia, the gland becomes smaller and firmer to the touch. It

remains extremely vascular. The capsule is thickened. The stroma, both inter- and intra-lobular, becomes denser and compresses the follicles. Colloid is absent. On section the gland has a dry, granular, gray-red-opaque appearance. Microscopically, the epithelial cells are at first of a uniform high columnar type with here and there an atypical cell mass. As the atrophy progresses more and more, the epithelial cells become irregular in size and shape and staining reactions. The epithelium loses its uniform arrangement in the follicles and piling up, desquamation and disintegration are seen in the same follicle along with mitotic figures. The nuclei are enlarged, often hyperchromatic, and quite variable in size, shape, and staining intensity. As the atrophic process continues, the follicles are further reduced by the cells' death and advancing sclerosis until they may appear as compressed nests of cells with or without the bare outlines of follicles. We have four mild examples of such glands in our exophthalmic goiter series in which, clinically, the severe and classical symptoms masked the definite though slight manifestations of myxedema. We have also had a specimen of this type of thyroid change referred to us with the histological diagnosis of probable cancer.

Such anatomical evidence of the inability of the cells to further grow and divide normally has long been looked on as a cell-exhaustion, the result of overwork and malnutrition, and since R. Hertwig and his pupils have produced and studied similar changes in the protozoan cell, it becomes probable that this is the true explanation.

In cretin pups we have observed thyroid changes similar to those just described and have been able to cause these atypical cells to return to the cuboidal or resting form with the accumulation of colloid in the follicles by the administration of small doses of iodin, and later, by partial removal of the gland, to produce a uniform and regular compensatory epithelial hyperplasia.

The process, therefore, whether occurring in exophthalmic goiter or in cretinism, is a premature cell death in spite of attempts to regenerate and is never observed in the early or vigorous stages of cell growth. It is of interest to note in this connection that Warthin[6] has described the same process of premature atrophy and fibrosis of lymph-glands in the lymphoid hyperplasia of status lymphaticus.

II. SECONDARY HYPERPLASIA

Clinically, the cases with secondary active hyperplasia are often spoken of as secondary exophthalmic goiter, while anatomically the term means only active hyperplasia developing from a colloid gland. These cases are much more common in goiter districts. In our series we have thus designated twenty-six cases. The number is probably not absolutely

6. Warthin: Arch. Pediat., 1909, xxvi, 597.

accurate since, as pointed out above, it most likely includes cases in which the primary or preceding hyperplasia had not returned to pure colloid goiter. The distinction, however, between primary and secondary hyperplasia is important, first, because it recognizes the fundamental conception of colloid goiter as the cured stage of an active hyperplasia and not as a degeneration, and secondly, because it offers a logical and simple explanation for many structural changes which have, in the past, served as a basis for theoretical discussion.

A. Developing Secondary Active Hyperplasias

Active hyperplasias developing from colloid glands do not differ from those developing from normal glands and all gradations from the colloid gland up to the marked hyperplasia occur. Their interpretation offers

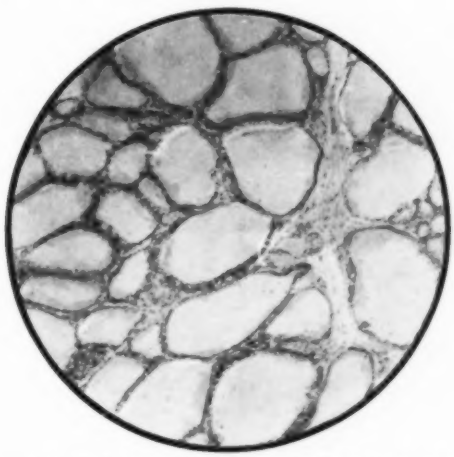

Fig. 1.—Normal thyroid (Case H—450; see Table 3). Note the rounded and moderately uniform size of the follicles; the homogeneous and uniform colloid; the cuboidal epithelium and the normal stroma.

more difficulties on account of the frequency of other morphological changes. Thus it is rare to see secondary hyperplasias in man free from other structural changes as hemorrhage, cyst formation, degeneration or tumors. Then, in addition, the presence of any or all of these conditions may modify or impair the reaction of the adjacent thyroid tissue, and one not uncommonly sees in these glands large central areas or it may be but a few enlarged follicles which fail to undergo active hyperplasia, while the peripheral zone shows the usual picture of increased blood-supply, decrease in colloid and columnar epithelium with infoldings and plications.

The essential anatomical changes are the same as those detailed for the primary hyperplasia and need not be repeated since all glands with extensive complicating changes were excluded.

B. Involutionary or Recovery or Colloid Stage

The growth of a secondary active hyperplasia may be arrested at any stage of its development and partially or completely return to colloid goiter again. The anatomical changes in this process are the reverse of those seen in the developing stage and identical with those detailed under "The involution of primary active hyperplasias." It may be pointed out here that this cycle of changes, characterized by developing hyperplasia followed by its involution, is common to all goiters and in all animals

Fig. 2.—Active thyroid hyperplasia of marked degree (Case H—427 as type; see Table 3). Note the irregular sized and distorted follicles with infoldings and plications of the lining epithelium; the regular and uniform, high columnar epithelium; the absence of true colloid and the generalized increase of stroma.

studied, and one may see the cycle repeating itself in the gland again and again as is illustrated in the thyroid changes with multiple pregnancies in man, or as can be produced experimentally in dogs by alternately giving and withholding iodin in conjunction with partial removal of the gland.

C. Exhaustion or Premature Atrophy or Myxedematous Stage

If the secondary hyperplasia is permitted to continue without periods of physiological rest, a series of changes may occur similar to those already described as occurring in the "Exhaustion stage of primary active hyperplasia." It is not so frequent, however, as in the primary group for

the reason that the individual has as a rule much more thyroid tissue with which to compensate. Nevertheless, it may occur. In our series of glands we did not recognize such an instance.

3. COLLOID GOITERS (SEE FIG. 3)

There are eighteen in our series. Colloid goiter is the nearest normal state, anatomically (and physiologically as well), to which actively hyperplastic thyroids may return. This involution, whether it occurs spontaneously or is induced by the action of iodin, is histologically the same. The general characteristics of pure colloid goiter are (1) decreased blood-supply as compared with that which is present in the active hyperplasia, (2) an accumulation of normal colloid in the enlarged follicles, (3) a return of the follicular epithelium to the normal cuboidal form. The

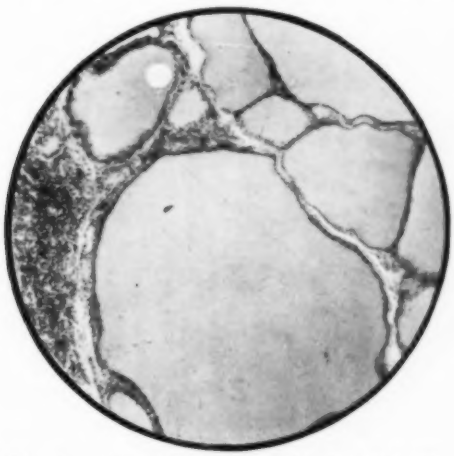

Fig. 3.—Colloid goiter (Case H—236; see Table 3). Note the great variation in the size of the follicles; their slightly irregular outlines; the normal cuboidal epithelium and the uniform, normally staining colloid. Note also the focus of lymphoid tissue in the stroma and its relation to the thyroid follicles.

histological details of these changes and of the process as a whole have already been published.[7]

In certain of the cases with colloid goiter no past history of iodin medication was obtained; in others such a history was definite, and in still others we have personally followed its administration and the resulting thyroid changes, so that we can positively state that iodin induces the same kind of changes in the active hyperplasia of exophthalmic goiter as in any other functional hyperplasia in any of the animals studied.

7. Marine and Lenhart: Bull. Johns Hopkins Hosp., 1909, xx, 131; The Archives Int. Med., 1911, vii, 506.

This biological reaction with iodin eliminates the formerly widely held opinion among pathological anatomists that the thyroid changes in exophthalmic goiter are specific and explains such cases as that reported by Shepherd and Duval[8] in which at the first operation the gland was in the state of active hyperplasia and at a later operation the gland was in the colloid state, or of such cases as that reported by MacCallum,[3] when at a first operation there was a mild degree of active hyperplasia and at a second operation there was a more marked hyperplasia. The size of colloid goiters is usually smaller than, but depends largely on, the preceding active hyperplasia and is therefore variable.

4. *ADENOMATA (SEE FIG. 4)*

Adenomata were present in eight cases, of which six were of the fetal adenoma types. In five, the entire lobe including the tumor was removed.

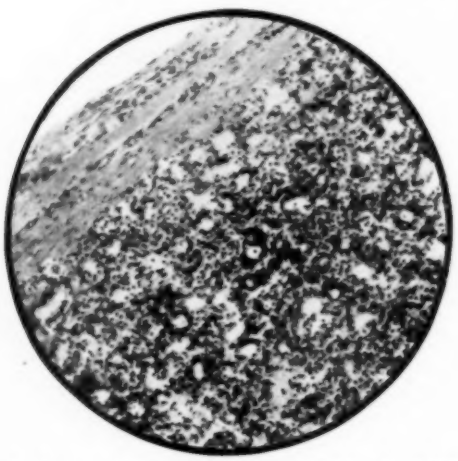

Fig. 4.—Fetal adenoma (Case H—220 x; see Table 3). Showing relation of capsule to parenchyma.

These glands have been grouped according to the anatomical structure of the non-tumor thyroid tissue which in three cases was that of normal colloid glands and in two cases, colloid glands. In the remaining three cases the tumors were enucleated. As pointed out in a previous paper adenomata do not occur in otherwise normal glands and the presence of colloid glands in the five instances of our series merely means that the preceding hyperplasia of the non-tumor thyroid tissue had returned to the colloid state either spontaneously or through the action of iodin, without notably affecting the tumors. The histological characteristics of both

8. Shepherd and Duval: Anns. Surg., 1909, l, 84.

the fetal and simple adenomata have been described elsewhere[9] and need not be repeated. Any direct relation of these tumors to the symptom-complex of exophthalmic goiter is doubtful since we have found several (seven in 216 autopsies) of these tumors at autopsy when no suspicion of thyroid disease existed and have also seen several specimens accidentally removed along with goiters from cases with no manifestations of exophthalmic goiter. Many authors have observed these tumors, in connection with exophthalmic goiter and Bloodgood[10] in this country has reported such cases, but came to the same general conclusion to which we have been led, viz., that the association is accidental and in no sense causal.

5. HIGHLY COMPLICATED GOITER

We will merely mention the four cases diagnosed as exophthalmic goiter, in which highly complicated old colloid goiters were removed. The structures were so disturbed by hemorrhage, cyst-formation, calcification, circumscribed tumor nodules, etc., that it was impossible to gain any conception of the relative importance of the several structural alterations.

II. Thymus, Spleen and Lymph-Glands

The changes in these organs are as striking and as constant as those of the thyroid. In the past, little importance has been attached to these tissues in describing the pathological anatomy of exophthalmic goiter, although the occurrence of changes has long been noted. During recent years the lymphoid hyperplasia has attracted much attention and to-day we are forced to give to these organs a place of equal importance in the pathological anatomy of exophthalmic goiter, to that held by the thyroid. There are observers who look on lymphoid hyperplasia as a complicating factor in exophthalmic goiter—preferring to speak of exophthalmic goiter *and* lymphatism—rather than as an integral part of the same process. The constancy with which lymphoid hyperplasia occurs in exophthalmic goiter and the definite parallelism between the degree of lymphoid hyperplasia and the thyroid hyperplasia in their progressive stages, cannot now be passed as accidental. Just as the thyroid hyperplasia is not specific for exophthalmic goiter, so also the lymphoid hyperplasia is not specific. Identical changes in the thymus, spleen and lymph-glands constantly occur in status lymphaticus and frequently in cretinism, myxedema, acromegaly, myasthenia gravis, epilepsy, achondroplasia, rickets and the so-called simple goiter.

1. THE THYMUS

While Markham first noted enlargement of the thymus in exophthalmic goiter, it was not until Marie in 1888 suggested that there might

9. Marine and Lenhart: The Archives Int. Med., 1911, vii, 506.
10. Bloodgood: Surg., Gynec. and Obst., 1906, ii, 121.

be a "revivescence" of the involuted thymus in exophthalmic goiter that more general interest was aroused. The more recent studies of Hart, Gierke, Thornebecke, Hektoen, Capelle, Warthin, Kocher and others have demonstrated the constancy of the thymic hyperplasia in exophthalmic goiter. The degree of hyperplasia present varies with the age of the patient, the duration and severity of the disease and most certainly with other still unknown factors. Thus, in young individuals the gland throughout is composed of elastic, grayish-pink and opaque tissue, while in older subjects there are usually accumulations of fat in the lobules, giving them a yellowish translucent appearance with patchy grayish areas of thymic tissue. Histologically, there are no distinctive features from the hyperplasia of status lymphaticus or myxedema or even the normal thymus.[11]

Whether regeneration of the involuted thymus occurs is difficult of actual demonstration. In support of Marie's view may be mentioned the fact (1) that the thymus in a markedly involuted state persists throughout life and (2) that the thymus hyperplasia seen in cases of exophthalmic goiter developing after 40 years of age usually has markedly reduced numbers of Hassall's corpuscles. This disproportion is probably due to the fact that Hassall's corpuscles, being only the atrophic vestiges of the thymic ducts, are incapable of regeneration.

II. SPLEEN

Splenic enlargement is the rule. This enlargement is in part due to the hyperplasia of the Malpighian corpuscles and the generalized sclerosis. The organ is firm to the touch. On section the Malpighian corpuscles are distinct and enlarged. The capsule and trabeculæ are thickened. Histologically there are no distinctive features by which the splenic enlargement in goiter may be separated from those seen in the *status lymphaticus* group.

III. LYMPH-GLANDS

The lymphoid tissue increase is general. It involves both the formed lymph-nodes and the small scattered nests of lymphocytes in the framework of several viscera, as the thyroid, liver and kidney. In all the cases of exophthalmic goiter with well-marked active thyroid hyperplasia, we have observed lymph foci in the thyroid stroma. These areas vary from small collections of lymphocytes to larger areas with well-formed germinal centers. They also vary with the degree of general lymphoid hyperplasia. The Peyer's patches and solitary follicles of the small intestine and colon respectively are enlarged. The tonsils are also frequently enlarged and adenoid growths in the nasopharynx are commonly seen. Histologically, the individual lymph-follicles appear normal. In older or

11. Warthin: In Osler and McCrae's Modern Medicine, Phila., 1908, iv, 789.

long-standing cases there is usually a general increase in the stroma which as Warthin[12] has pointed out may go on to connective tissue overgrowth with atrophy and disappearance of the parenchyma cells. It will be recalled that the thyroid may undergo a similar sclerosis and atrophy of the parenchyma cells in the late stages of compensatory hyperplasia. The lymphoid elements of the bone-marrow may be increased just as occasionally occurs in lymphatism.

III. The Nervous System

The lesions thus far reported are neither constant nor suggestive of any specific gross abnormality. In the brain small hemorrhages and areas of softening are occasionally noticed. In the medulla, areas of softening and punctate hemorrhages have also been found, but with no constancy of occurrence or location. Atrophy and sclerosis of one or both restiform bodies and of the solitary tract are likewise only occasionally present. In the cervical sympathetic trunks atrophy of the ganglion cells in one or in all the cervical ganglia accompanied by fibrosis, pigmentation and small round cell-infiltration have been reported, but in a majority of the specimens examined, whether at autopsy or at operation, no lesions could be made out. The lesions of the peripheral nervous system and the spinal cord can be ascribed to the general state of nutrition and the accidental association with other diseases. The absence, however, of any constant gross lesion does not preclude the probability that the central nervous system is profoundly affected, but suggests, as Gowers[13] states, "that the morbid state of the nervous system is one of that finer cell-nutrition that still baffles our means of investigation."

IV. Heart

The heart hypertrophies with the development of active thyroid hyperplasia (goiter) in all animals thus far studied, including the fish, dog, sheep, ox and man. The cardiac hypertrophy in general varies with the size of the hyperplastic thyroid. The most marked and perhaps simplest type of heart hypertrophy is seen in cretins (lambs, pups and children). Taking the goitrous cretin pup as the most familiar example, it is found that the whole musculature of the heart is hypertrophied. The ventricles appear relatively more enlarged than the auricles. Both ventricles are also dilated. Histologically, the muscle is of normal appearance. The heart valves are normal. The inferior vena cava is not enlarged, while the superior cava and all its communications leading from the thyroid are dilated and their walls hypertrophied. Clinically, venous pulsation is nearly constantly present in these pups and may usually be

12. Warthin: In Osler and McCrae's Modern Medicine, 1908, iv, 778.
13. Gowers: Diseases of the Nervous System, Phila., 1888, p. 1211.

recognized at some distance from the animal, thus showing the extent of the insufficiency of the auricular orifice of the superior cava. The pulmonary artery is also enlarged. The pulmonary veins are not particularly enlarged. The aorta is enlarged as far as the left carotid branch, and it is not unusual to see the left carotid artery as large as the aorta beyond this branch. Both carotid trunks appear to terminate in the superior thyroid arteries and the internal carotids and the remaining branches of the external carotids appear as relatively small branches of these main trunks. In dogs with large goiters the much enlarged arteries are therefore mainly the thyroid arteries. We have also been able to follow the regressive changes in these arteries as the hyperplasia involutes to its colloid or quiescent state and to note the gradual lessening of the size of these arteries and the development of endo-arterial thickening with calcification (in man and sheep particularly) in the late stages. We have also observed under such conditions that the heart becomes smaller. This is the simplest manifestation of the so-called "goiter heart." It resembles in all respects the hypertrophies resulting from work, and there appears to be no reason for regarding it as different.

In human goiter the early anatomical changes as above described for dogs occur, but in the long-standing cases in adults, and particularly in exophthalmic goiter, secondary changes affecting the valves, the arteries, the myocardium and the conductivity of impulses often develop. As there are many views concerning the significance of these late changes, it would take us too far afield to consider them here.

Concluding, then, we would again emphasize that the cretinoid states in the very young animals offer the simplest and best material for the study of the uncomplicated "goiter heart," and that such studies indicate that the condition is primarily a work-hypertrophy. The secondary and subsequent changes are more intricate and perhaps dependent on a failing nutrition.

V. Skeletal Muscles

Askanazy[14] has called attention to the general disturbance in the nutrition of the skeletal muscles. In his four cases he found, in association with the atrophy of the fibers and the loss of normal striation, fat deposits in and around the fibers which he has likened to the fatty metamorphosis seen in progressive muscular dystrophy. The occurrence of fatty changes in the eye-muscles was known to von Recklinghausen and Buschan. Profound muscular weakness is often present in this disease without corresponding reduction in the muscle bulk, and it is possible that the fatty metamorphosis is in some way related to this phenomenon.

14. Askanazy: Deutsch. Arch. f. klin. Med., 1896, lxi, 118.

VI. Bone

The development of osteomalacia during the course of exophthalmic goiter has been observed by von Recklinghausen, Haemig, Revilliod, von Jaksch and H. Ratky, Hoennicke and others. The association of thyroid hyperplasia with endemic osteomalacia is well known, and it is doubtful whether the osteomalacia developing in exophthalmic goiter is of any greater or different significance than the osteomalacia with goiter in general. Both the goiter and the bone changes are probably secondary to some more general disturbance. The more prominent bone changes are decalcification, increased vascularity of the periosteum and widening of the Haversian capillaries.

VII. Liver

In a significant number of the long-standing cases coming to autopsy, cirrhosis of the liver has been observed. In the gross such livers are reduced in volume, sometimes smooth, sometimes slightly granular and again distinctly hobnailed. The extent of the connective tissue increase varies from a slight thickening of the portal spaces to well-marked fibrous bands. The liver-cells usually exhibit some degree of fatty metamorphosis.[15]

VIII. Blood

The occurrence of high grades of chlorotic anemia is probably less common now than formerly. Bigelow[16] mentions its frequent association with the patients he saw in Boston and adds that in London in 1857 nothing was more common than "Pale, anemic, weak girls with goiter and staring eyes." Chvostek[17] has also remarked on the association. To-day, while slight degrees of the chlorotic type of anemia[18] are often present and while true chlorosis is usually associated with thyroid hyperplasia and often with mild manifestations of the exophthalmic goiter symptom-complex (Virchow and Stengel), there does not appear to be any special relation between the exophthalmic goiter syndrome and the changes in the red blood-tissue. There are distinct and relatively constant, but in no sense specific, alterations in the ratios of the white blood-cells. The total number of white blood-cells is but slightly altered. As Sawyer, Kocher, Buehler, Kappis, Van Lier, Carpi and others have shown, the change is a decrease in the number of the polymorphonuclear

15. There have been six post-mortem examinations of fatal cases at Lakeside Hospital (Autopsy Nos. 474, 777, 966, 1131, 1171, 1211). There were four males aged 65, 55, 44 and 20 years, and two females aged 56 and 31 years. In five of the cases there was well-marked thickening of Glisson's capsule throughout the liver and in four a diagnosis of atrophic cirrhosis was made.

16. Bigelow: Boston Med. and Surg. Jour., 1859-60, lxi, 37.

17. Chvostek: Wien. klin. Wchnschr., 1893, vi, 487.

18. Roth: Deutsch. med. Wchnschr., 1910, xxxvi, 258.

leukocytes and an increase in the lymphocytes and mononuclear leukocytes. Van Lier[19] finds in forty-five cases of true exophthalmic goiter that averages of from 8 to 10 per cent. of all white blood-cells are mononuclear leukocytes and that averages of from 35 to 45 per cent. of all white blood-cells are lymphocytes. Extremes of 16 per cent. of mononuclears and 57 per cent. of lymphocytes have been reported. We have found that there is a close parallelism between the percentage of mononuclear cells in the circulating blood and the extent of the active lymphoid and thyroid hyperplasia. The blood examination is, therefore, the most accurate clinical means of judging the extent of active lymphoid hyperplasia and, while in no sense specific for exophthalmic goiter, is a fair index of the severity of the disease.

3. *RELATION OF IODIN CONTENT TO GLAND STRUCTURE*

The published observations concerning thyroid iodin in its relation to exophthalmic goiter have shown no uniformity. The causes of these widely different results are the same as those which caused the widely

TABLE 1.—IODIN CONTENTS, NORMAL SERIES

Anatomical Groups	No. of Cases	Iodin per gm. of Dried Thyroid in mg. Extremes	Mean	Average
Normals and Normal-Colloids	5	4.00	1.54	1.92
		0.96	....	....
Normal-early glandular hyperplasia	1	....	....	0.77
Normal-moderate marked glandular hyperplasia	5	0.81	0.38	0.51
		0.31	....	....
Normal-marked glandular hyperplasia	11	0.58	0.12	0.22
		0.00	....	....

TABLE 2.—IODIN CONTENTS, COLLOID SERIES

Anatomical Groups	No. of Cases	Iodin per gm. of Dried Thyroid in mg. Extremes	Mean	Average
Pure Colloids	18	4.61	2.24	2.24
		1.00	....	....
Colloid-early glandular hyperplasia	6	0.84	0.71	0.72
		0.61	....	....
Colloid-early moderate glandular hyperplasia	3	0.92	0.77	0.67
		0.31	....	....
Colloid-moderate glandular hyperplasia	3	0.82	0.55	0.58
		0.37	....	....
Colloid-moderate marked glandular hyperplasia	3	0.82	0.34	0.49
		0.32	....	....

different conclusions concerning the anatomical changes. Iodin variations are more quickly and more easily produced than structural variations. Both iodin content and gland structure are subject to rapid natural changes in all animals, and when in addition to these natural changes one has to consider the artificial variations from one cause and

19. Van Lier: Beitr. z. klin. Chir., 1910, lxix, 201.

another to which human thyroids as a group, and exophthalmic goiter thyroids in particular, are subject, it becomes evident that no fundamental or general conclusions can be drawn until one has collected a large series of iodin determinations, and at the same time has a general knowledge of the natural and experimentally induced variations in man and the lower animals. Then, by excluding all glands whose structural changes are so manifold as to be irreducible to some single type, it is possible to draw conclusions concerning the relation of iodin to structure.

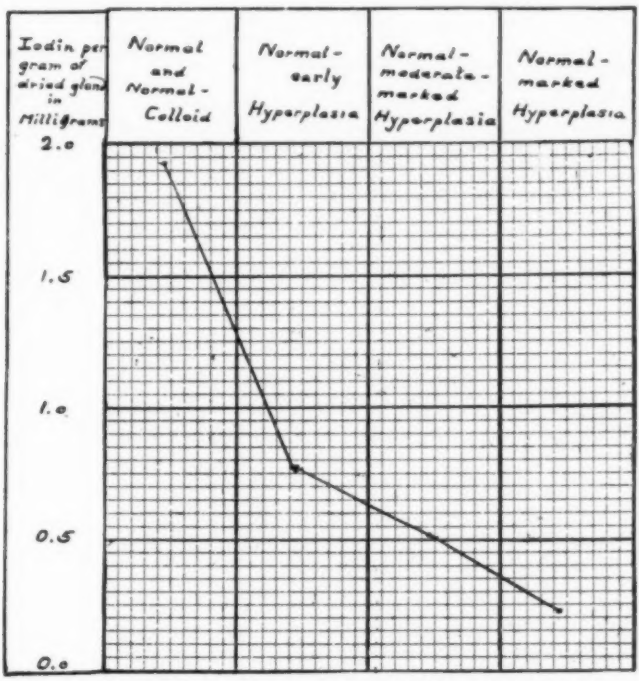

Fig. 5.—Normal series; average iodin contents.

In our series there were sixty-nine glands in which such comparisons were justifiable. Eleven of these glands have been excluded from the accompanying tables (Tables 1 and 2) for the reason that iodin had been given so recently (two to three weeks) that at the time of removal they were still actively hyperplastic. In three, adenomata only were removed.

An examination of these tables shows that the normal or normal-colloid and the pure colloid glands have the highest percentage iodin contents, and that the marked hyperplasias have the lowest iodin contents. In the accompanying curves (Figs. 5 and 6), made from the average

percentage iodin contents, this relation is more graphically shown. Here one notes the great drop in the percentage iodin content from the normal or colloid gland which occurs before noticeable histological changes take place. This great drop is similar to that constantly found in the dog, sheep, pig, ox and human thyroid series previously reported,[20] and we ascribe the same significance to it as was then given for thyroids in general, viz., "that the percentage of iodin which normal or colloid

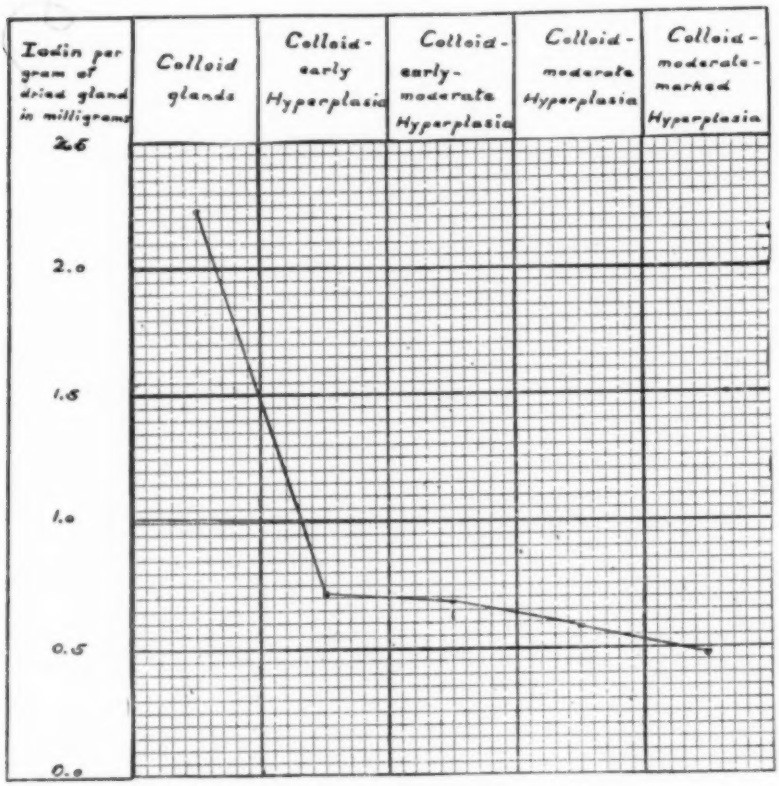

Fig. 6.—Colloid series; average iodin contents.

thyroids may contain is variable, but the percentage necessary to maintain normal or colloid gland structure is quite constant." Passing to the several degrees of active hyperplasia, it is seen that, just as in all the lower animals and in the non-exophthalmic human series, there is a more gradual but progressive lessening of the percentage iodin content, which

20. Marine and Lenhart: THE ARCHIVES INT. MED., 1909, iv, 440.

reaches its lowest amount in the marked hyperplasias both of the normal and colloid series.

The eight cases of exophthalmic goiter with adenomata were grouped as follows: six with the fetal adenomata and two with the simple adenomata. The iodin contents of the six fetal adenomata were 0.0, 0.0, 0.01, 0.08, 0.08, and 0.14 mg. per gram of dried tumor. The two simple adenomata contained 0.25 and 0.38 mg. iodin per gram of dried substance. In three of these cases the tumor alone was removed and in five a portion of the non-tumor thyroid tissue in addition was removed. A comparison of the percentage iodin contents of the tumors with those of the surrounding original thyroid tissue in each corresponding case (Table 3), shows that no relation exists between them, even in those cases (two) known to have received iodin medication. The surrounding thyroid tissue in all five cases was very high in iodin, while the tumors were very low in iodin. Thus, while the original thyroid tissue is capable of taking up iodin rapidly, the tumor tissue has no such capacity, and we have taken advantage of this fact as an aid in separating tumors from physiological hyperplasias, both clinically and anatomically.[21]

Summing up the relation of iodin to thyroid structure in exophthalmic goiter, it is seen that the same relations exist as were found true for other animals' thyroids and for the non-exophthalmic human thyroids as well, viz., that the percentage iodin content varies inversely with the degree of active epithelial hyperplasia. Hence, the changes in the iodin content, just as the morphological changes in exophthalmic goiter, are only those common to all developing goiters in all the animals examined.

It becomes increasingly difficult to draw accurate conclusions concerning the relation of iodin to thyroid structure as one passes from the lower animals to man and from human thyroids in general to exophthalmic goiter, for the reason (1) that human goiters rarely continue their course for long undisturbed, and (2) that the thyroid is easily and quickly modified both as to structures and iodin content in a variety of ways which reach their numerical acme and complexity in exophthalmic goiter. Some of the major factors known to affect both the structure and the iodin content are: rest, diet, drugs, intercurrent infection, locality, age and the duration of the disease.

Experimental observations on the effect of the administration of iodin in exophthalmic goiter are necessarily disconnected. There were eleven cases (one colloid-moderate-marked hyperplasia, seven colloid-moderate hyperplasias and three colloid-early hyperplasias) in which the patients were treated with iodin from one to three weeks prior to operation. In all of the cases, the iodin contents of the thyroids were markedly raised, and in none had complete involution to the colloid state occurred. There

21. Marine and Lenhart: THE ARCHIVES INT. MED., 1911, vii, 506.

Series Number, History Number, Sex, Age	Major Complaint. Date of Admission	Goiter. Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Before Operation	Pulse Before Operation 1. Admission 2. High 3. Low 4. Average
H-427 4956 P.W.S. Male 33	Goiter, tachycardia. Jan. 5, 1910.	Six months, soft, symmetrical, pulsation, well nourished.	No mention of.	Muscular weakness, sweating, insomnia, tremor.	+ ?	6	130 130 80 95
H-382 4441 P.W.S. Male 16	Goiter, dyspnea, tachycardia. May 25, 1909.	Eight yrs. iodin, disappeared; reappeared 18 mos., soft symmetrical, well nourished.	Loss of hair.	Muscular weakness, sweating, irritability, tremor.	+	7	145 150 100 120
H-437 5152 P.W.S. Male 42	Dyspnea, nervousness. March 29, 1910.	Five months, very small, symmetrical, firm, thrill, fair nutrition.	Loss of body and scalp hair.	Muscular weakness, diarrhea, tremor, restlesness.	+	2	90 115 90 105
H-232 3575 P.W.S. Male 43	Nervousness, weakness. March 27, 1908.	Fifteen months, very small, symmetrical, firm, thrill, emaciated.	No mention of.	Muscular weakness, tremor, sweating.	+	4	85 120 68 87
H-441 4920 P.W.S. Female 32	Goiter, weakness. Dec. 26, 1909.	Eight months, soft, symmetrical, small, well nourished.	Marked general loss of hair.	Skin flushes, sweats, muscular weakness, tremor.	6	5	160 160 90 115
H-364 4116 P.W.S. Female 31	Weakness, tremor, palpitation. Jan. 4, 1909.	17 years, cured by iodin; reappeared 5 yrs. ago; operated; relapsed 3 years ago; lobe small, firm, emaciated.	General loss of hair; general brownish pigmentation.	Mental depression, muscular weakness, tremor, diarrhea.	+	2	110 120 100 110
H-251 .... P.W.S. Male 24	Goiter, sweating. May 19, 1908.	Six years, small, soft, symmetrical, well nourished.	No mention of.	Muscular weakness, tremor, sweats, diarrhea.	+	4	110 115 85 100
H-267 .... P.W.S. Male 20	Palpitation. July 19, 1908.	Seven months, soft, small, thrill, symmetrical, poor nutrition.	Loss of body hair.	Extreme muscular weakness, diarrhea, tremor, melancholia.	+	20	125 140 80 120
H-401 4626 P.W.S. Female 33	Goiter, extreme nervousness. July 26, 1909.	Six months, soft, symmetrical, lost 55 pounds in six months.	Loss of hair.	Constant vomiting, sweats, diarrhea, muscular weakness.	+	57	130 160 95 140
H-214 3495 P.W.S. Female 37	Nervousness, palpitation. Feb. 17, 1908.	Two years, soft, symmetrical, moderate enlargement, well nourished.	Skin dry; patchy pigmentation; loss of hair general.	Melancholia, extreme weakness.	+	5	130 140 120 125
H-222 3543 P.W.S. Female 54	Goiter, weakness. March 16, 1908.	Three weeks, small, soft, symmetrical.	No mention of.	Melancholia, 8 months extreme muscular weakness, tremor.	0	5	130 130 80 110
.... 3369 P.W.S. Female 23	Shortness of breath, palpitation. Oct. 17, 1907.	Six months, soft, medium sized, symmetrical, well nourished.	No mention of.	Skin flushes, irritability, diarrhea, weakness.	+	34	130 180 70 120
H-443 5322 P.W.S. Female 56	Goiter, nervousness. May 22, 1910.	For many years symmetrical, firm, poorly nourished.	No mention of.	Weakness, tremor, palpitation.	+	6	120 120 90 100
H-388 4467½ P.W.S. Female 27	Goiter, nervousness. June 6, 1909.	*	*	*	+	13	*

* Record lost

Pulse After Operation. 1. High. 2. Low. 3. Average.					Temperature Before Operation.	Temp. After Oper'n. 1, high; 2, low; 3, av.				Anatomical Diagnosis	Iodin per Gram of Dried Gland in Milligrams	Outcome (immediate)	Remarks Portion of Gland Removed
First Day	Second Day	Third Day	Average at Discharge	Time in Hospital After Operation	1. Admission High 2. High 3. Low 4. Average	First Day	Second Day	Third Day	Aver. Normal on Day Given				
...	...	...			99	.....	.....	.....		Marked glandular hyperplasia.	Trace (not measurable).	Improved.	Hemithyroidectomy.
135	130	115			99	104.5	104.6	103.5					
130	110	105	95	24 days	98	101	102.5	102	9th				
132	120	110			98.7	103	103.5	103					
...	...	...			99.3	.....	.....	.....		Marked glandular hyperplasia.	Trace (not measurable).	Improved.	Double partial lobectomy.
150	180	185			99.7	102	104	106					
130	140	145	95	19 days	97.8	101	103.6	103.6	8th				
140	160	160			99	101.5	103.7	104.5					
...	...	...			99.5	.....	.....	.....		Marked glandular hyperplasia; fibrosis.	0.08	Improved.	Hemithyroidectomy.
120	115	105			99.5	101	100.5	100					
105	95	95	95	11 days	98	100	100	99.5	6th				
110	105	100			98.7	100.5	100.3	99.8					
...	...	...			98.5	.....	.....	.....		Marked glandular hyperplasia; fibrosis.	0.12	Improved.	Partial double lobectomy.
162	140	102			98	102	102	101.5					
110	90	70	85	8 days	98	98	98	99	6th				
130	105	85			98.2	100	100	100					
...	...	...			98	.....	.....	.....		Marked glandular hyperplasia.	0.13	Improved.	Hemithyroidectomy.
145	150	130			95	102	101.5	100.5					
120	140	110	105	15 days	98	100	100.5	99.5	12th				
130	145	120			98.6	101.5	101	100					
...	...	...			99	.....	.....	.....		Marked glandular hyperplasia, fibrosis and myxedematous atrophy.	0.13	Died.	Ligation of artery; small bit of lobe removed.
150	180	...			99	100	102.5	.....					
130	170	...		2 days	98.2	98	99	.....	...				
135	178	...			99	99.5	101	.....					
...	...	...			99.2	.....	.....	.....		Marked glandular hyperplasia.	0.28	Improved.	Hemithyroidectomy.
160	120	125			99.2	102.4	102	102					
105	100	90	70	15 days	98	100.7	101	100.5	9th				
120	110	115			98.1	101	101.5	101					
...	...	...			99.2	.....	.....	.....		Marked glandular hyperplasia.	0.21	Died.	Hemithyroidectomy; autopsy.
195	200	150	160		102	104	103	106	108.5				
160	150	90	75	4 days	98	101	99	99.5	103				
170	180	135	105		99	103	102	104	108				
...	...	...			101.5	.....	.....	.....		Marked glandular hyperplasia.	0.31	Died.	Hemithyroidectomy.
...	...	...			101.5	.....	.....	.....					
...	...	...	...	.....	98	.....	.....	.....	...				
...	...	...			98.6	.....	.....	.....					
...	...	...			98	.....	.....	.....		Marked glandular hyperplasia, fibrosis, myxedematous atrophy.	0.54	Died.	Hemithyroidectomy.
180	200	...			98	103	107	.....					
160	165	...	...	2 days	97	100	104	.....	...				
170	180	...			97.5	102	.....	.....					
...	...	...			100	.....	.....	.....		Marked glandular hyperplasia; fibrosis.	0.58	Died.	Partial double lobectomy.
160	...	...			100	99	.....	.....					
132	...	...	...	1 day	98	.....	.....	.....	...				
150	...	...			99	.....	.....	.....					
...	...	...			99.4	.....	.....	.....		Moderate-marked glandular hyperplasia.	0.31	Died.	Hemithyroidectomy.
...	...	...			100	.....	.....	.....					
...	...	...	...	3 hrs.	97	105	.....	.....	...				
220	...	...			98.4	107.5	.....	.....					
...	...	...			98.5	.....	.....	.....		Moderate-marked glandular hyperplasia.	0.58	Improved.	Hemithyroidectomy.
130	112	103			100.5	101	101	99.8					
110	100	96	105	16 days	98	100	99.5	99	9th				
120	110	100			98.5	100.5	100	99.2					
...	...	...			.....	.....	.....	.....		Moderate-marked glandular hyperplasia.	0.38	Improved.	Hemithyroidectomy.
...	...	...	*		.....	.....	.....	.....					
				12 days	.....	.....	.....	.....	...				
					.....	.....	.....	.....					

* Record lost.

TABLE 3 (*Continued*).—CLINICAL OBSERVATIONS

Series Number, History Number, Sex, Age	Major Complaint. Date of Admission	Goiter. Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Before Operation	Pulse Before Operation: 1. Admission 2. High 3. Low 4. Average
H-433 5147 P.W.S. Female 47	Nervousness, tachycardia. March 29, 1910.	Six years, soft, symmetrical, small, emaciated.	General pigmentation; loss of hair.	Extreme muscular weakness, sweating, tremor.	+	11	130 140 100 120
H-270 3775 P.W.S. Male 35	Headache, vomiting. July 15, 1908.	Four weeks following influenza, small, symmetrical, firm, poorly nourished.	No mention of.	Gradual general weakness following influenza.	0	6	120 125 90 105
H-259 .... P.W.S. Male 22	Loss of nervous control. June 9, 1908.	No thyroid enlargement, firm, well nourished.	No mention of.	General neurasthenia.	0	4	90 95 72 90
H-450 5369 P.W.S. Female 20	Nervousness, tachycardia. Sept. 20, 1910.	Palpable thyroid, firm, well nourished.	No mention of.	Tremor, muscular weakness, sweats.	+ ?	2	104 104 80 95
H-402 4663 P.W.S. Male 22	Nervousness, tachycardia. Sept. 20, 1909.	Palpable thyroid, firm, well nourished.	Loss of hair.	Nervousness, diarrhea.	0	5	90 90 70 80
H-434 5200 P.W.S. Female 45	Nervousness, tachycardia. April 7, 1910.	Slight enlargement of right lobe two years, firm, well nourished.	No mention of.	Menopause, weakness, tremor.	+	2	84 84 65 72
H-239 ..... Female 45	Nervousness, weakness. April 21, 1908.	Two years, small mass on right side, firm, well nourished.	No mention of.	Muscular weakness, sleeplessness, nervousness.	0	2	100 112 90 100
H-348 4098 P.W.S. Female 27	Dysmenorrhea, weakness. Dec. 5, 1908.	Palpable thyroid, firm, well nourished.	No mention of.	Irritable neurasthenia.	0	2	128 128 80 85
H-429 4973 P.W.S. Male 16	Dyspnea. Jan. 26, 1910.	Nine months, symmetrical, firm, well nourished.	Loss of hair.	3 months, noticed tremor, sweating, weakness.	0	2	95 95 63 70
H-371 4256 P.W.S. Female 40	Goiter, dyspnea. Feb. 26, 1909.	Twenty-six years, symmetrical, firm, well nourished.	No mention of.	Dizziness, gradual weakness for last six years.	0	1	100 100 85 92
H-372 4309 P.W.S. Female 37	Tumor of neck. March 5, 1909.	Seven years, mainly on right side, firm, well nourished.	No mention of.	Tremor, irritability.	0	1	90 107 90 100
H-212 3487 P.W.S. Female 29	Goiter. Feb. 4, 1908.	Ten years, firm, symmetrical, well nourished.	No mention of.	Weakness, sweating, hysteria.	0	2	80 100 70 90

Pulse After Operation. 1. High. 2. Low. 3. Average.					Temperature Before Operation.	Temp. After Oper'n. 1, high; 2, low; 3, av.				Diagnosis	Iodin per Gram of Dried Gland in Milligrams	Outcome (immediate)	Remarks
First Day	Second Day	Third Day	Average at Discharge	Time in Hospital After Operation	1. Admission High 2. High 3. Low 4. Average	First Day	Second Day	Third Day	Aver. Normal on Day Given	Anatomical			Portion of Gland Removed
...	...	...			101	.....	.....	.....		Moderate-marked glandular hyperplasia.	0.69	Died.	Hemi-thyroid-ectomy; weight, 35 gm.
...	...	...			101	.....	.....	.....					
...	...	...	...	9 hrs.	98	.....	.....	.....	...				
180	...	...			98.8	101	.....	.....					
...	...	...			98	.....	.....	.....		Moderate-marked glandular hyperplasia.	0.81	Improved.	Hemi-thyroid-ectomy.
180	190	140			99	100.5	100	100					
120	120	110	80	10 days	98	99	99	98	4th				
150	160	125			98.2	100.2	99.2	99					
...	...	...			98	.....	.....	.....		Normal early glandular hyperplasia.	0.77	Improved.	Partial double hemi-thyroid-ectomy; wt. of tissue removed, 13 gm.
130	137	135			99	102	102	99.5					
110	110	120	95	11 days	97	100.5	101	98	5th				
120	120	130			98	101	101.5	99					
...	...	...			100.4	.....	.....	.....		Normal thyroid.	1.54	Improved.	Hemi-thyroid-ectomy; wt. of portion removed, 12 gm.
132	120	110			100.4	101.6	100	99					
100	105	85	80	14 days	97.5	98.3	99	98	4th				
110	112	95			98.6	99.5	99.5	98.6					
...	...	...			99	.....	.....	.....		Normal thyroid.	4.00	Improved.	Hemi-thyroid-ectomy; wt. of gland, 16.5 gm.
130	120	130			99	102.5	101	101					
110	105	100	90	13 days	97.5	100	100	100	6th				
120	110	115			98	101	101	100.5					
...	...	...			99.5	.....	.....	.....		1. Normal colloid (senile type).	0.96	Improved.	Hemi-thyroid-ectomy; wt. of tissue removed, 10 gm.
100	105	85			99.5	99.5	99.6	99					
90	90	78	82	21 days	98	99	99	98	4th	2. Fetal adenoma.	0.01		
98	100	80			98.2	99.3	99.5	98.8					
...	...	...			98.6	.....	.....	.....		1. Normal colloid.	1.19	Improved.	Partial hemi-thyroid-ectomy.
150	125	120			99	100.2	101.2	101.2		2. Fetal adenoma.	0.14		
120	112	110	80	14 days	98.6	99.1	99.6	100	8th				
125	120	115			98.6	100	100.5	100.5					
...	...	...			99.5	.....	.....	.....		1. Normal colloid.	1.92	Improved.	Hemi-thyroid-ectomy.
115	120	120			99.5	100.5	101	101		2. Fetal adenoma.	0.00		
95	115	100	80	22 days	97.5	99	100	100	7th				
112	117	110			98.6	100	100.5	100.5					
...	...	...			100	.....	.....	.....					Hemi-thyroid-ectomy.
125	130	110			100	103	104	103		Pure colloid.	1.00	Improved.	
100	100	95	90	12 days	97	101	102	101	7th				
110	115	100			98.7	102	103	102					
...	...	...			98.2	.....	.....	.....		Pure colloid.	1.08	Improved.	Hemi-thyroid-ectomy.
130	120	115			98.4	102	100.5	100					
110	97	95	100	12 days	98	100	100	98	4th				
125	110	105			98.2	101	100.3	99					
...	...	...			98.2	.....	.....	.....		1. Pure colloid.	1.15	Improved.	Hemi-thyroid-ectomy.
135	133	125			98.2	103	103.4	104		2. Simple adenoma.	0.25		
120	120	120	90	35 days	97.5	99	102	102	11th				
125	125	123			98	101	103	103.5					
...	...	...			98	.....	.....	.....		Pure colloid.	1.28	Improved.	Hemi-thyroid-ectomy.
110	155	140			99	103	102.5	101.5					
90	90	120	85	12 days	97	99	101	100	6th				
100	120	130			98.2	101	101.5	100.5					

TABLE 3 (*Continued*).—CLINICAL OBSERVATIONS

Series Number, History Number, Sex, Age	Major Complaint. Date of Admission	Goiter. Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Before Operation	Pulse Before Operation: 1. Admission 2. High 3. Low 4. Average
H-447 .... P.W.S. Female 17	Goiter, palpitation. Sept. 8, 1910.	Six months, right lobe larger, firm, well nourished.	No mention of.	Mother dead, of exophthalmic goiter; weak, irritable.	0	1	130 130 72 75
H-409 4805 P.W.S. Female 55	Nervousness. Nov. 3, 1909.	Ten years, small, firm, symmetrical, well nourished.	Loss of hair.	Neurotic for years, sweating, tremor.	0	3	115 115 90 100
H-... 3255 P.W.S. Female 31	Palpitation. Sept. 8, 1907.	Twenty years, firm, symmetrical, well nourished.	No mention of.	Periods of melancholia, weakness, tremor.	0	4	95 95 70 80
H-406 4778 P.W.S. Female 38	Goiter, nervousness. Oct. 22, 1909.	Sixteen years, small, firm, symmetrical, well nourished.	No mention of.	Tremor, excitable for eighteen months.	+	14	120 130 80 95
..... 3308 P.W.S. Female 29	Rheumatism, palpitation, organic heart lesion. Nov. 6, 1907.	Six months, hard, small, symmetrical, well nourished.	No mention of.	Always nervous, broken compensation of heart.	+	1	70 90 70 85
..... 3456 P.W.S. Female 22	Goiter, abdominal pain. Jan. 7, 1908.	Eight years, firm, symmetrical, well nourished.	No mention of.	Always nervous, "blues."	0	3	100 100 84 92
H-411 4725 P.W.S. Female 20	Goiter, nervousness. Oct. 16, 1909.	Four years, firm, symmetrical, adenoids, well nourished.	No mention of.	Always nervous, palpitation.	0	4	108 108 90 100
H-445 5487 P.W.S. Male 56	Weakness, mental deterioration. Sept. 8, 1910.	18 mos. ago noticed small symmetrical enlargement; firm, emaciated.	Loss of hair; general pigmentation.	Profound weakness, mental aberration.	+	2	108 108 87 95
H-204 .... G.S.S. Female 22	Goiter. Jan. 5, 1908.	Eight years, firm, large, emaciated, well nourished.	None.	Typical example of relative cure of exophthalmic goiter.	+	2	96 110 88 95
H-390 4596 P.W.S. Female 18	Tumor of neck. Aug. 17, 1909.	Three years, symmetrical, firm, well nourished.	Slight loss of scalp hair.	Somewhat nervous and weak.	0	2	136 136 110 115
H-359 .... P.W.S. Female 32	Goiter, nervousness. Jan. 21, 1909.	Seven months, soft, small, symmetrical, well nourished.	No mention of.	Paroxysmal palpitation and nervous weakness.	0	5	110 120 72 90
H-203 3441 P.W.S. Female 24	Hoarseness, goiter. Dec. 30, 1907.	Ten years, symmetrical, small, firm, well nourished.	No mention of.	Tremor for four months.	+	5	100 120 68 90
H-419 4823 P.W.S. Female 37	Goiter, nervousness. Nov. 11, 1909.	Twenty years, right side larger, firm, well nourished.	No mention of.	Weakness, excitability, slight tremor.	0	11	160 160 95 105
H-236 3612 P.W.S. Female 19	Goiter, nervousness. April 6, 1908.	Four years, symmetrical, firm, well nourished.	No mention of.	Weakness, tremor, sweating, flushing.	+	5	135 155 88 110

Pulse After Operation. 1. High. 2. Low. 3. Average.					Temperature Before Operation.	Temp. After Oper'n. 1, high; 2, low; 3, av.				Anatomical Diagnosis	Iodin per Gram of Dried Gland in Milligrams	Outcome (immediate)	Remarks Portion of Gland Removed
First Day	Second Day	Third Day	Average at Discharge	Time in Hospital After Operation	1. Admission 2. High 3. Low 4. Average	First Day	Second Day	Third Day	Aver. Normal on Day Given				
...	...	...			99.5	.....	.....	.....		Pure colloid.	1.54	Improved.	Hemithyroidectomy.
104	100	95			99.5	100.5	100.2	99.5					
90	85	70	75	11 days	98	99.8	99	98.6	4th				
95	35	80			98.6	100	99.5	99					
...	...	...			98.6	.....	.....	.....		Pure colloid.	1.85	Improved.	Partial thyroidectomy.
160	165	160			99	103	103	102.5					
130	135	140	100	25 days	98	101	101	100.5	7th				
150	150	150			98.2	102	102	101					
...	...	...			99.6	.....	.....	.....		Pure colloid.	1.88	Died.	Hemithyroidectomy.
160	...	...			99.6	102.5	.....	.....					
140	...	...	...	1 day	97.7	100	.....	.....	...				
150	...	...			98	102	.....	.....					
...	...	...			98	.....	.....	.....		Pure colloid.	2.00	Improved.	Hemithyroidectomy.
160	170	165			98.6	102	101	101.5					
135	140	140	105	13 days	97	99	100	101	10th				
150	160	150			98	100	100.5	101.5					
...	...	...			98.6	.....	.....	.....		Pure colloid.	2.18	Improved.	Hemithyroidectomy.
95	90	90			98.8	100	100	99.5					
80	80	80	85	12 days	98.2	99	99	98	3d				
90	85	85			98.6	99.5	99.5	98.5					
...	...	...			99	.....	.....	.....		Pure colloid.	2.31	Improved.	Partial thyroidectomy.
135	135	120			99	102	102	102					
110	120	105	100	18 days	98	101	101	99.5	10th				
120	125	115			98.2	101.5	101.5	100					
...	...	...			98	.....	.....	.....		Pure colloid.	2.31	Improved.	Hemithyroidectomy.
160	145	135			99	101	101	100.5					
90	130	125	115	9 days	97.8	98	100	98	7th				
100	140	130			98.6	99	100.5	100					
...	...	...			98	.....	.....	.....		Pure colloid.	2.38	Died.	Hemithyroidectomy; arterial ligation in May,'10.
130	...	...			98.6	.....	.....	.....					
85	...	...	...	1 day	97	.....	.....	.....	...				
128	...	...			97.5	102	.....	.....					
...	...	...			98	.....	.....	.....		Pure colloid.	2.58	Improved.	Hemithyroidectomy; fed iodin 7 months; chloroform.
140	143	143			99	101.5	101.8	101.2					
120	120	120	85	12 days	99.8	100	100.2	98	3d				
130	130	130			98.6	101	101	100					
...	...	...			99	.....	.....	.....		Pure colloid.	2.74	Improved.	Partial double thyroidectomy.
135	160	140			99	100.5	101	101.5					
130	115	130	105	12 days	98	99	98	98	9th				
131	135	135			98.6	99.5	100	100					
...	...	...			98.5	.....	.....	.....		1. Pure colloid.	2.77	Improved.	Hemithyroidectomy; fed iodin.
112	120	120			99.6	100.4	100.8	100.2		2. Fetal adenoma.	0.08		
100	93	109	105	11 days	97.5	99	100	99	4th				
108	108	112			98.2	100	100.4	100					
...	...	...			99	.....	.....	.....		Pure colloid.	3.09	Improved.	Hemithyroidectomy; fed iodin.
152	130	120			99.5	101	102	100.5					
110	115	95	80	15 days	98	100	100	99	6th				
120	120	105			98.6	100.5	101	99.5					
...	...	...			99	.....	.....	.....		Pure colloid.	3.69	Improved.	Partial double lobectomy; typical lymphoid infiltration.
130	145	160			99	101.5	102	102					
120	120	145	120	15 days	98	99	100	100	5th				
125	130	155			98.6	101	101	101					
...	...	...			98	.....	.....	.....		Pure colloid.	4.61	Improved.	Hemithyroidectomy; fed iodin 5 months.
130	145	142			98	102	101.5	102					
120	120	130	105	14 days	98	101	100	100	8th				
128	140	135			98	101.5	101	100.5					

TABLE 3 (*Continued*).—CLINICAL OBSERVATIONS

Series Number, History Number, Sex, Age	Major Complaint. Date of Admission	Goiter. Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Before Operation	Pulse Before Operation: 1. Admission 2. High 3. Low 4. Average
H-431 5023 P.W.S. Female 35	Goiter, nervousness. Feb. 18, 1910.	Fifteen years, nodular, firm, well nourished.	No mention of.	Slight general weakness.	+ +	1 1	95 95 85 90
H-425 4943 P.W.S. Female 24	Abdominal pain, nervousness. Jan. 5, 1910.	Several years, symmetrical, mod. firm, well nourished.	No mention of.	Migraine tremor.	0 0	1 1	96 96 85 86
H-211 3486 P.W.S. Female 36	Goiter. Jan. 28, 1908.	Eighteen months, firm, small, symmetrical, well nourished.	No mention of.	Always had "blues," irritable, tremor.	0 0	2 2	90 90 70 80
..... 3461 P.W.S. Female 20	Nervousness. Jan. 9, 1908.	Three years, firm, symmetrical, well nourished	Pigmentation.	Tremor four years, excitable.	+ ?	7 7	115 115 85 95
H-262 3483 P.W.S. Female 32	Tumor of neck. Jan. 30, 1908.	Eleven years, firm, symmetrical, well nourished.	No mention of.	Muscular weakness, tremor.	0 0	2 2	95 98 75 85
H-418 4801 P.W.S. Female 23	Goiter, nervousness. Nov. 12, 1909.	Many years, firm, symmetrical, well nourished.	No mention of.	General weakness.	0 0	4 4	90 100 80 90
H-349 4107 P.W.S. Female 40	Headache. Nov. 24, 1908.	Nine months, symmetrical, small, soft, well nourished.	Loss of hair; slight pigmentation.	Weakness, headache, excitability, vomiting.	+ +	23 23	130 135 100 120
H-201 3426 P.W.S. Female 25	Nervousness, palpitation. Nov. 11, 1908.	Seven years, small, firm, symmetrical, well nourished.	No mention of.	Tremor for seven years, sweating, excitable.	+ +	27 27	100 130 90 100
H-391 4569 P.W.S. Female 33	Tumor of neck. July 30, 1909.	Duration ? Firm, small, symmetrical, well nourished.	No mention of.	Mild general nervousness.	0 0	4 4	115 115 85 95
H-397 4579 P.W.S. Female 14	Goiter. Aug. 4, 1909.	Eight years, soft, large, symmetrical, well nourished.	No mention of.	Very slight general nervousness.	0 0	14 14	110 110 60 80
H-444 5490 P.W.S. Female 36	Nervousness, palpitation, goiter. Aug. 22, 1910.	Twenty-five years, soft, symmetrical, well nourished.	No mention of.	Nervousness, Excitable twelve years, muscular weakness.	0 0	2 2	98 98 80 85
H-439 5210 P.W.S. Female 16	Nervousness, goiter. May 21, 1910.	Two years, soft, symmetrical, well nourished.	Loss of hair.	Palpitation, sweating, tremor.	+ +	1 1	90 110 80 90
H-369 4234 P.W.S. Male 22	Goiter. Feb. 8, 1909.	Two years, soft, symmetrical, well nourished.	No mention of.	None of note.	0 0	3 3	88 88 72 80
H-394 4506 P.W.S. Female 19	Headache, nervousness. July 16, 1909.	Duration ? Well nourished.	No mention of.	Three months, weakness, sweating, tremor.	0 0	5 5	106 100 70 75
..... 3381 P.W.S. Female 54	Goiter and breast tumor. Nov. 1, 1907.	Two years, mod. firm, symmetrical, emaciated.	No mention of.	General weakness and nervousness.	0 0	8 8	100 140 90 115

Pulse After Operation. 1. High. 2. Low. 3. Average.					Temperature Before Operation.	Temp. After Oper'n. 1, high; 2, low; 3, av.				Anatomical Diagnosis	Iodin per Gram of Dried Gland in Milligrams	Outcome (immediate)	Remarks Portion of Gland Removed
First Day	Second Day	Third Day	Average at Discharge	Time in Hospital After Operation	1. Admission High 2. Low 3. Average	First Day	Second Day	Third Day	Aver. Normal on Day Given				
...	...	...			98.5	.....	.....	.....		Colloid-early glandular hyperplasia.	0.62	Improved.	Hemi-thyroid-ectomy.
100	100	90			98.6	100.5	100	99					
85	95	80	85	9 days	98	98.5	99	98	3d				
90	90	85			98.5	100	99.5	98.6					
...	...	...			99.8	.....	.....	.....		Colloid-early glandular hyperplasia.	0.62	Improved.	Hemi-thyroid-ectomy.
96	100	90			99.8	102	101	100.5					
87	87	87	90	21 days	99.5	100.5	100.5	100	7th				
90	90	88			99.6	101	100.8	100.1					
...	...	...			98.2	.....	.....	.....		Colloid-early glandular hyperplasia.	0.65	Improved.	Hemi-thyroid-ectomy.
105	90	90			98.2	100.5	99.5	99.1					
85	75	75	85	18 days	97	99	98	99	5th				
90	85	82			98	99.2	99	99					
...	...	...			99.5	.....	.....	.....		Colloid-early glandular hyperplasia.	0.77	Improved.	Hemi-thyroid-ectomy.
150	140	120			99.5	101.5	101	99.5					
135	115	110	95	13 days	98	101	100	99	6th				
145	125	115			98.6	101.5	100.5	99.2					
...	...	...			98.2	.....	.....	.....		Colloid-early glandular hyperplasia.	0.83	Improved.	Hemi-thyroid-ectomy.
100	110	105			98.2	100.5	99	100.5					
85	100	95	90	15 days	97	99	98	98	4th				
95	100	100			98	100	98.5	99					
...	...	...			98.6	.....	.....	.....		Colloid-early glandular hyperplasia.	0.85	Improved.	Hemi-thyroid-ectomy.
110	130	120			99.5	101	100.5	100					
100	105	95	95	12 days	98	99.5	100	98.6	7th				
105	115	110			98.6	100	100	99.2					
...	...	...			98.5	.....	.....	.....		Colloid-early glandular hyperplasia.	1.85	Improved.	Hemi-thyroid-ectomy; fed Iodin 2 weeks.
160	150	148			99.5	103	103.5	103.5					
135	140	130	115	18 days	97.5	100	102	101	8th				
150	148	140			98.6	101.5	102.5	102					
...	...	...			98.2	.....	.....	.....		Colloid-early glandular hyperplasia.	4.12	Improved.	Hemi-thyroid-ectomy; fed Iodin 3 weeks.
155	155	140			100	101	101.5	101.5					
135	135	120	90	21 days	97	99	100	99.5	7th				
145	140	130			98	100	101	100					
...	...	...			99	101.5	.....	.....		Colloid-early glandular hyperplasia.	4.15	Improved.	Hemi-thyroid-ectomy; no history of Iodin R!?
160	140	140			99	100	101.5	101.5					
130	130	120	100	18 days	98	101	100	100	...				
150	135	125			98.6	.....	100.5	101					
...	...	...			100.5	.....	.....	.....		Colloid-early moderate glandular hyperplasia.	0.31	Improved.	Hemi-lobectomy.
110	120	125			100.5	99.6	101	100					
90	105	95	100	7 days	98	98.6	99	99	4th				
100	110	110			98.6	99	99.5	99.5					
...	...	...			98.5	.....	.....	.....		Colloid-early moderate glandular hyperplasia.	0.77	Improved.	One lobe and isthmus; entire portion of other lobe.
120	112	105			99	101	100	99.5					
100	100	90	90	19 days	98	99	99	98	8th				
115	105	100			98.5	100	99.5	99					
...	...	...			99.5	.....	.....	.....		Colloid-early moderate glandular hyperplasia.	0.92	Improved.	Hemi-thyroid-ectomy.
125	120	100			99.5	100	101	.....					
110	100	80	80	13 days	98.5	99.5	98.5	.....	2d				
115	110	95			99	100	99.6	.....					
...	...	...			98	.....	.....	.....		Colloid-moderate glandular hyperplasia.	0.37	Improved.	Hemi-thyroid-ectomy.
140	130	105			99	103	102.5	101					
72	110	95	85	28 days	97.5	99	100.5	99.5	13th				
120	120	100			98.1	101	101	100					
...	...	...			98.8	.....	.....	.....		Colloid-moderate glandular hyperplasia.	0.55	Improved.	Hemi-thyroid-ectomy.
120	120	100			99	101.5	101	99.5					
110	90	80	85	4 days	97.5	100	99	98.4	3d				
115	100	90			98.6	101	100	99					
...	...	...			99	.....	.....	.....		Colloid-moderate glandular hyperplasia.	0.82	Improved.	Hemi-thyroid-ectomy.
160	140	125			100.5	103	102	99					
140	105	110	95	21 days	98	100	99	98	3d				
150	130	120			98.2	101.5	100	98.6					

TABLE 3 (*Continued*).—CLINICAL OBSERVATIONS

Series Number, History Number, Sex, Age	Major Complaint. Date of Admission	Goiter. Duration, Consistency, Symmetry, General Nutrition	Myxedema Manifestations	Prominent Nervous Features	Exophthalmus	Days in Hospital Before Operation	Pulse Before Operation: 1. Admission 2. High 3. Low 4. Average
H-265 .... P.W.S. Female 57	Goiter, tachycardia. Aug. 22, 1908.	Many years, irregular nodules, firm, fair nutrition.	No mention of.	Weakness, nervousness, arrhythmia.	+	8	110 125 80 115
H-386 4490 P.W.S. Female 59	Tumor of neck. June 13, 1909.	35 years, up and down course, nodular, firm, well nourished.	No mention of.	Tremor, weakness.	0	11	120 130 105 115
H-381 1026 G.S.S. Female 42	Exophthalmic goiter. May 28, 1909.	Six years, soft, symmetrical, well nourished.	No mention of.	Extreme muscular weakness, tremor.	+	4	115 115 70 90
H-292b 9493 G.S.S. Male 44	Graves' disease. Sept. 7, 1908.	Left lobe enlarged, soft, poor nutrition.	Loss of hair; dry skin.	Cardiac arrhythmia, weakness.	+	1	90 115 82 90
H-416 4817 P.W.S. Female 22	Goiter, nervousness. Nov. 1, 1909.	Six months, small, soft, symmetrical, well nourished.	Loss of hair.	Nervousness, excitability, sweating.	+	15	125 125 100 110
H-292a 9310 G.S.S. Male 44	Graves' disease. June 22, 1908.	Seven months, small, firm, symmetrical, fair nutrition.	Dry skin; loss of hair.	Muscular weakness, mental depression, restlessness.	+	26	100 115 70 80
H-269 3894 P.W.S. Female 21	Palpitation. July 27, 1908.	16 mos., just after typhoid fever soft, symmetrical, poorly nourished.	Loss of hair.	Muscular weakness, restlessness.	+	14	130 135 80 90
H-392 4596 P.W.S. Female 30	Goiter, vomiting. Oct. 9, 1909.	Nine months, large, firm, symmetrical, poorly nourished.	Loss of hair; dry skin.	Nervousness, tremor, vomiting, weakness.	+	23	140 140 100 105*
H-264 3824 P.W.S. Female 19	Weakness, tachycardia. July 3, 1908.	One year, soft, symmetrical, well nourished.	No mention of.	Always nervous, weak, diarrhea.	+	8	140 140 70 100
H-374 4898 P.W.S. Female 26	Nervousness. Feb. 27, 1909.	Six months soft, symmetrical, well nourished.	No mention of.	Tremor, diarrhea, excitability.	+	19	140 140 90 125
H-215 3529 P.W.S. Female 29	Palpitation, sweating. Feb. 18, 1908.	Two years, pregnancy, firm, symmetrical, well nourished.	No mention of.	Muscular weakness, excitability, tremor, diarrhea.	0	4	145 145 103 115
H-408 4692 P.W.S. Female 36	Goiter, nervousness. Oct. 5, 1909.	Sixteen years, enlarged isthmus, firm, well nourished.	No mention of.	Nervous for two years.	0	1	85 90 70 80
H-417 4837 P.W.S. Female 28	Goiter, nervousness. Nov. 19, 1909.	Six years, firm, right lobe enlarged, well nourished.	No mention of.	General nervousness.	0	2	130 130 90 110
..... 3343 P.W.S. Female 30	One-sided goiter. Oct. 21, 1907.	Twelve years, firm, right side, well nourished.	No mention of.	General weakness, slight dyspnea.	0	1	80 82 75 78

* After one week.

Pulse After Operation. 1. High. 2. Low. 3. Average.					Temperature Before Operation.	Temp. After Oper'n. 1, high; 2, low; 3, av.				Anatomical Diagnosis	Iodin per Gram of Dried Gland in Milligrams	Outcome (immediate)	Remarks Portion of Gland Removed
First Day	Second Day	Third Day	Average at Discharge	Time in Hospital After Operation	1. Admission High 2. Low 3. Average	First Day	Second Day	Third Day	Aver. Normal on Day Given				
...	...	...			98	.....	.....	.....		Colloid-moderate glandular hyperplasia.	1.15	Died.	Hemi-thyroid-ectomy.
...	...	...			102	.....	.....	.....					
...	...	...	...	1 day	98	.....	.....	.....	...				
185	...	...			100.5	105	.....	.....					
...	...	...			99.5	.....	.....	.....		Colloid-moderate glandular hyperplasia.	1.31	Improved.	Partial double lobectomy.
130	128	138			99.5	101	102.2	101.5					
100	120	120	108	20 days	98	100	101	100	11th				
125	125	125			98.8	100.5	102	101					
...	...	...			99	.....	.....	.....		Colloid-moderate glandular hyperplasia.	1.31	Died.	Partial double lobectomy.
...	...	...			99	.....	.....	.....					
...	...	...	...	16 hrs.	98	.....	.....	.....	...				
212	...	...			98.6	106	.....	.....					
...	...	...			99	.....	.....	.....		Colloid-moderate glandular hyperplasia.	1.85	Improved.	One half of remaining lobe.
142	144	128			99	101.5	102.5	101.2					
120	123	88	85	19 days	97.3	100	101.2	100.4	7th				
130	130	106			98.2	101	101.8	100.8					
...	...	...			99	.....	.....	.....		Colloid-moderate glandular hyperplasia.	2.00	Improved.	Hemi-thyroid-ectomy.
160	160	140			100	102	102	100					
100	140	120	120	17 days	97	98	100	99	4th				
150	150	135			98.6	101	101	99.5					
...	...	...			99	.....	.....	.....		Colloid-moderate glandular hyperplasia.	2.02	Improved.	Hemi-thyroid-ectomy.
170	150	110			99.5	101	101	99.5					
130	120	90	95	14 days	98.0	99	99	98.5	4th				
135	135	100			98.2	100	100	99					
...	...	...			98	.....	.....	.....		Colloid-moderate glandular hyperplasia.	4.03	Died.	Partial thyroid-ectomy. Fed Iodin one week!
...	...	...			98.6	.....	.....	.....					
...	...	...	...	3 hrs.	98	.....	.....	.....	...				
180	...	...			98.2	107	.....	.....					
...	...	...			98.6	.....	.....	.....		Colloid-moderate-marked glandular hyperplasia.	0.32	Improved.	Hemi-thyroid-ectomy.
140	145	140			98.6	101	101.5	101.5					
120	125	125	85	19 days	98	100	100.5	100	4th				
130	135	130			98.6	100.5	101	101					
...	...	...			101	.....	.....	.....		Colloid-moderate-marked glandular hyperplasia.	0.34	Improved.	Hemi-thyroid-ectomy.
128	128	104			101	100.5	100.2	99.5					
110	110	100	80	18 days	98	100	99.5	98	4th				
115	115	102			99	100.2	100	99					
...	...	...			99.6	.....	.....	.....		Colloid-moderate-marked glandular hyperplasia	0.82	Improved.	Hemi-thyroid-ectomy; weight, 58 gm.
172	170	168			99.6	101.2	102	100.5					
135	140	148	130	18 days	97.5	99	101	99.5	11th				
160	160	160			98.6	101	101.5	100					
...	...	...			99	.....	.....	.....		Colloid-moderate-marked glandular hyperplasia.	1.60	Improved.	Hemi-thyroid-ectomy. Fed Iodin!
160	145	140			99.5	101	100.5	101					
140	140	120	100	18 days	97.5	99	100	98	4th				
150	142	130			98.2	100	100	100					
...	...	...			98	.....	.....	.....		Fetal adenoma (cells highly irregular —cancer?)	0.00	Improved.	Adeno-mectomy.
105	112	115			98.6	101	100.5	100					
95	95	95	80	12 days	97.5	99.5	99	100	7th				
100	105	105			98.6	100	100	100					
...	...	...			99.5	.....	.....	.....		Colloid adenoma.	0.38	Improved.	Adeno-mectomy.
135	155	142			99.5	101.5	101.5	100.5					
95	135	130	95	21 days	98.4	97.5	100.5	99.2	7th				
120	140	138			98.6	99	101	100					
...	...	...			99	.....	.....	.....		Fetal adenoma.	0.08	Improved.	Adeno-mectomy.
165	95	100			99	101.2	100.5	100.5					
90	85	70	75	11 days	98.2	100	99.5	99	5th				
98	90	85			98.6	100.5	100	99.5					

were four cases which had received iodin for periods varying from two months to eighteen months, and in all complete involution to the colloid state was present at the time of the operation. We can, therefore, reasonably conclude that the active hyperplasia of exophthalmic goiter has the same characteristic of rapidly taking up iodin that characterizes all other active functional thyroid hyperplasias, and also that iodin induces a similar series of morphological changes in the exophthalmic goiter hyperplasia as in other active thyroid hyperplasias, and that these changes are histologically identical with those occurring in spontaneous involution (recovery).

4. *RELATION OF PULSE-RATE TO GLAND STRUCTURE*

A tabulation of the pre-operative and postoperative pulse-rates of the sixty-nine patients is given in the large table (Table 3). We have recorded the length of time in the hospital before operation, the pulse on admission, the highest, the lowest and the average pulse records during this time. Postoperative, we have recorded the highest, lowest and average pulse-rates for the first three days, the average pulse-rate at discharge and the length of time in the hospital after operation. We believe these records should accompany all case reports, for it is by taking into account these features that an accurate idea of the types of cases, surgically treated at the various clinics, may be gained. Such tabulations bring out many features of interest and significance. Thus, it will be noticed that the pulse-rates on admission and the highest pulse-rates before operation are closely related, while the average pulse-rates are usually much lower. The higher pulse-rate on admission is a manifestation of the general nervous instability and of the loss of vagus control, while the much lower average pulse-rate illustrates the effect of rest and the extent of the recovery of vagus control.

There are such differences between the highest and the lowest pulse-rates even in the most severe cases that only the mean or average rate gives a fair conception of the cardiac activity. Thus, in our extreme cases the average for the series was 110 beats per minute, although there were individual high averages of 140, 125, 120, etc. In order to demonstrate whether any relation exists between thyroid structure and the pulse-rate, we have charted the average pulse-rates of the normal and colloid series both before and after operation (Figs. 7 and 8).

In the normal series it is seen that there is a general relation between thyroid structure and the average pulse-rates. Thus, the average pulse-rates before operation are the lowest in those cases with normal glands (eighty-two per minute) and the highest (104 per minute) in the marked hyperplasias. The same relation tends to hold through the postoperative reaction as well. The difference between the pulse-rates of the cases with

normal thyroids and of those with markedly hyperplastic glands is of slight degree only, while the anatomical differences are extreme. Another feature of the pulse-rate curve is that the postoperative reaction usually reaches its extreme height in from twenty-four to forty-eight hours, then, in favorable cases it falls rapidly during the next three or four days and then continues at a more constant rate. In our cases the average pulse-rate at discharge corresponded closely with the average pulse-rate before operation. Thus, objectively the cardiac activity after operation and up

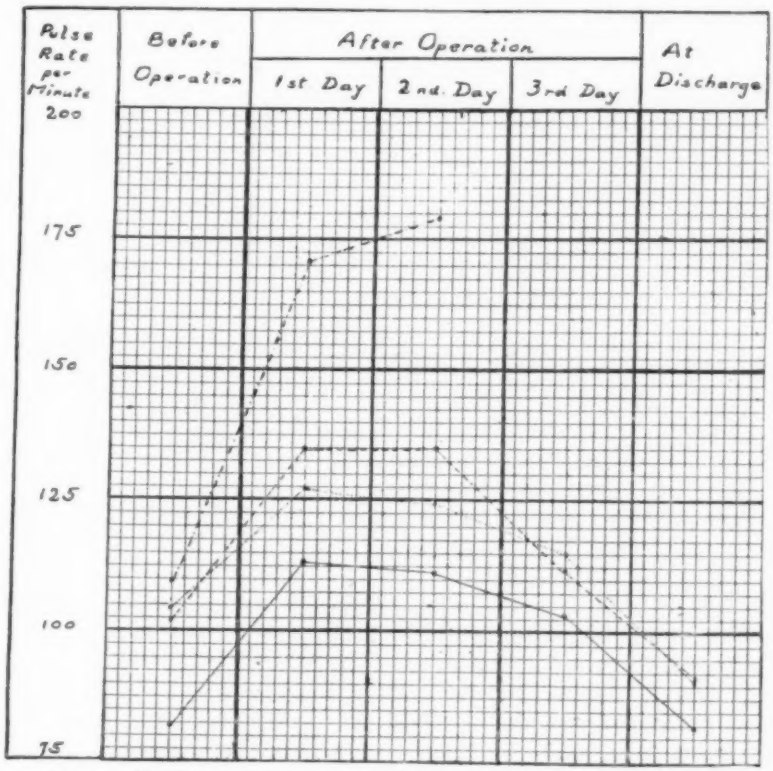

Fig. 7.—Normal series average pulse-rates. Plain line indicates normal thyroids. Line of dashes indicates moderate marked glandular hyperplasia. Finely dotted line indicates marked glandular hyperplasia. Line of dots and dashes indicates fatal cases.

to the time of discharge shows no noteworthy decrease from the average obtaining before operation. On the other hand, many of the patients subjectively feel a sense of cardiac relief, but as Graham Lusk has well said, "subjective sensations cannot be used as scientific criteria."[22]

22. Lusk, Graham: Science of Nutrition, Phila., 1906, p. 244.

Passing to the colloid series, the same striking features are present as have been pointed out for the normal series, viz., the pulse-rate to a very slight extent increases with the degree of active hyperplasia; the average pulse-rate before operation closely conforms with the average pulse-rate at discharge from the hospital and the postoperative rise describes the same type of curve.

Summing up the relation of the pulse-rates to the degree of active thyroid hyperplasia both in the normal and colloid series, it is seen that a slight parallelism exists, but the differences between the pulse-rates of the normal or colloid glands and of the most marked active hyperplasias are so slight as to bear no suggestion of any cause or effect relation. This

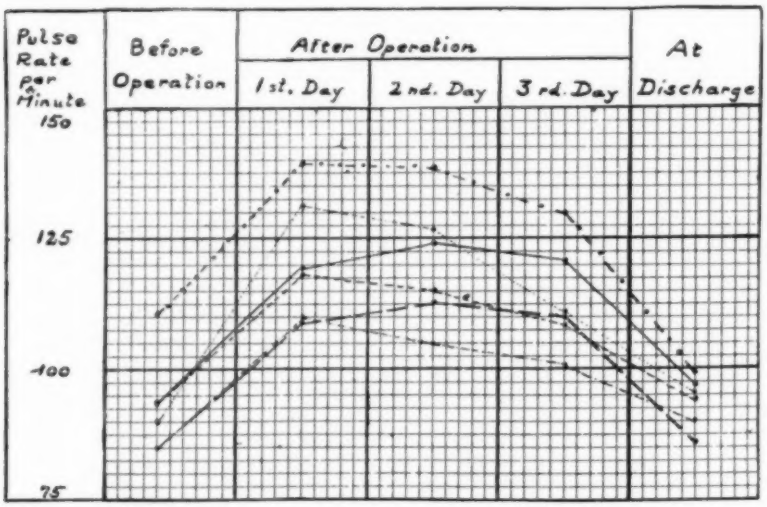

Fig. 8.—Colloid cases; average pulse-rates. Plain line indicates colloid glands. Line of dashes indicates colloid early glandular hyperplasia. Line of dashes and dots indicates colloid early moderate glandular hyperplasia. Dotted line indicates colloid moderate glandular hyperplasia. Line of dashes and circles indicates colloid moderate marked glandular hyperplasia. Line of long dashes indicates adenomata.

is the more striking on account of the widely held view that the thyroid secretion is a direct causal factor in the cardiac reaction. If any relation exists the objective evidence would tend to indicate a hyposecretion rather than a hypersecretion, since the pulse-rate bears no relation to the amount of secreting surface and a negligible relation to the histological structure of the gland. Also the histological structure and the iodin content may

be reversed in a given case, as will be mentioned later, without necessarily producing any modification of the cardiac activity, and adenomata may be associated with the same pulse reaction as ordinary hyperplasia.

It does not appear from the evidence at present available that the explanation of the cardiac activity is so superficial or simple as either a thyroid-hypersecretion or hyposecretion would indicate, but that both the cardiac activity and the thyroid reaction are parallel manifestations consequent on some more general and remote disturbance.

5. RELATION OF TEMPERATURE TO GLAND STRUCTURE

The temperature on admission, the highest, the lowest and the average temperature before operation; also the highest, lowest and average temperatures for the first three days following operation are recorded in Table 3. We have also added the total number of days of pyrexia following operation for each case.

These temperatures are for the most part oral and, therefore, only of relative value. The average temperatures before operation are approximately normal in the several anatomical groups of each series. The temperatures on admission are often somewhat elevated and it frequently happens that they coincide with the highest temperatures before operation, just as was true of the pulse-rates. True fever, after rest in bed is established, is exceedingly rare in uncomplicated cases, as many observers have pointed out. The subjective sensation of fever is very common.

The postoperative rise is usually quite abrupt. It reaches its height on the second day and in favorable cases gradually falls to an average of normal in from six to eight days (average). The temperature perhaps tends to be higher in the cases with marked thyroid hyperplasia than in the cases with normal or colloid glands, just as was noted with the pulse-rates, but the differences are too slight for a suggestion of any causal relation between gland structure and temperature reaction. The slightly higher temperatures associated with the more marked hyperplasias are probably parallel phenomena and indicative of a more severe type of disease. The pulse and temperature reactions after operation constitute the so-called "manifestations of hyperthyroidism"; that is, they are believed to be due to an exces of "toxic" thyroid secretion. The evidence for this hypothesis is at present inadequate. Both the temperature and pulse reactions point toward some more profound disturbance in the finer nutrition of the nerve-centers controlling these activities than could be explained by acute variations in the amount of thyroid secretion discharged from the gland.

6. RELATION OF EXOPHTHALMOS TO THYROID STRUCTURE, TO MORTALITY AND TO THE DISEASE IN GENERAL

Exophthalmos was recorded as present in thirty-five and as absent in thirty-four cases. Arranging the cases according to the anatomical divisions of the thyroid, it is found that exophthalmos was present in one of eight cases with adenomata, in two of five cases with normal or normal-colloid glands, in six of eighteen cases with colloid goiters and in twenty-seven of forty-three cases with active hyperplasia. Thus, exophthalmos was neither absent from any of the anatomical divisions nor present in all the cases of any single division. The greatest number of positive cases (both abolute and percentage) occurs in the group of active hyperplasias. On further analysis it is found that the frequency of exophthalmos in this series increases as the degree of active thyroid hyperplasia increases, both in the colloid and in the normal series. Exophthalmos was present in ten and absent in two of the fatal cases.

So far as this series of cases is concerned, one may say that exophthalmos is a highly inconstant feature. A. Kocher[23] in a series of seventy-four cases found exophthalmos in sixty-three. The personal factor, the liberality of the observer in diagnosing exophthalmic goiter and the natural facial outlines in many patients are conditions that materially modify the frequency of exophthalmos in any individual series. Only a most general relation exists between the incidence of exophthalmos and the degree of thyroid hyperplasia. Some observers have considered exophthalmos as dependent on the thyroid hyperactivity and cite the hyperthyroidization observations of Ballet and Enriquez[24] and of Notthafft,[25] who claim to have reproduced the symptom-complex of exophthalmic goiter in a dog and in a man, respectively, by feeding them excessive amounts of thyroid gland. While symptomatically hyperthyroidization may to some extent simulate the symptom-complex of exophthalmic goiter, it is biochemically quite different. The one might be looked on as an artificial excess of the normal secretion, while the other could not have a closer resemblance than that of a quantitative excess of an abnormal secretion.[26]

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23. Kocher, A.: Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1902, ix, 1.

24. Ballet and Enriquez: Semaine Méd., 1894, xiv, 66.

25. Notthafft: Centralbl. f. inn. Med., 1898, xix, 353.

26. In a previous publication (Marine and Williams: THE ARCHIVES INT. MED., 1908, i, 349) it was shown that the hyperplastic thyroid takes up iodin rapidly from inorganic and organic salts of iodin and from feeding thyroid. The general symptoms produced depend on the form and the amount of iodin given and on the anatomical state of the thyroid at the time of its administration. Overfeeding with desiccated or fresh sheep's thyroid produces the same general symptoms whether the thyroid is normal, colloid or hyperplastic, while iodin or its inorganic salts tends to produce these symptoms only in those cases

The facts that exophthalmos may be present either with the thyroid normal or with any degree of active thyroid hyperplasia, and that there may be marked thyroid hyperplasia without exophthalmos, point strongly against the view that thyroid hyperplasia is etiologically related to exophthalmos and toward the view that both phenomena are parallel, though often not synchronous, manifestations of a more fundamental and obscure nutritional disturbance.

7. *THE RELATION OF EXOPHTHALMIC GOITER TO MYXEDEMA*

In our series of sixty-nine patients four (Nos. 214, 222, 232, 364) had distinct anatomical changes characteristic of premature or myxedematous atrophy supervening in marked hyperplasias. In two of the patients there was well-marked general pigmentation with loss of scalp and body hair. In the other two no mention was made of these features. In the first two cases there was also dryness of the skin of the legs and arms, with sweating of the palms of the hands and soles of the feet (personal observations). Three died following operation with high temperatures and pulse-rates.

Owing to the fact that one seldom sees mention of this important and relatively frequent late manifestation in exophthalmic goiter, we would urge again the importance of very careful inquiry and examination of all cases of exophthalmic goiter coming under observation in order to detect clinically these very mild and very early manifestations of supervening myxedema, as well as careful anatomical examinations of the thyroid for the characteristic histological changes.

Ord[27] was perhaps the first to point out that myxedema was a natural sequel rather than a complication of exophthalmic goiter. More recently C. P. Howard,[28] West,[29] Dock[30] and ourselves[31] have emphasized this view.

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with very large, actively hyperplastic thyroids. These symptoms are increased appetite, loss of weight, diarrhea, becoming bloody in the late stages, weakness and sometimes coma before death. We have never observed any noteworthy increase in heart-rate or rise of body temperature or thyroid enlargement or exophthalmos in dogs, following such experiments. Cunningham (Jour. Exper. Med., 1898, iii, 148) in his much earlier and more extensive studies on "Experimental Thyroidism" was unable to reproduce in any of the animals used a condition resembling exophthalmic goiter by feeding thyroid gland, and at that time clearly pointed out the inadequateness of a hyperthyroidization theory in explaining the essential features of exophthalmic goiter. Recently Carlson, Rooks and McKie (Proc. Am. Physiol. Soc., 1911, xxvii, 13) have reported their experiments with feeding thyroid to a large series of animals with the same results reported by Cunningham and ourselves.

27. Ord: Brit. Med. Jour., 1885, i, 896.

28. Howard, C. P.: Jour. Am. Med. Assn., 1907, xlviii, 1226.

29. West: St. Bartholomew's Hosp. Rep., 1906, xlii, 9.

30. Dock: In Osler's Modern Medicine, Phila., 1909, vi, 437.

31. Marine and Lenhart: Relation of Iodin to the Structure of Human Thyroids, THE ARCHIVES INT. MED., 1909, iv, 440.

We have collected reports of cases by twenty-four observers and, as Hirschl[32] suggests, the cases may roughly be divided into two groups, (1) myxedema occurring during and (2) myxedema occurring after exophthalmic goiter. This grouping is purely clinical. The thyroid insufficiency starts when thyroid hyperplasia starts and may develop rapidly, as in cases reported by Osler,[33] Sollier,[34] Jolly[35] and others, in which case the severe manifestations of both symptom-complexes are nearly synchronous, or slowly, as in cases reported by Williams,[36] Gautier[37] and others, in which case the overlapping of the two syndromes is less complete.

It is of significance that myxedema never precedes but accompanies or follows exophthalmic goiter, and also, as pointed out by Gowan,[38] that the incidence of myxedema of adults as regards sex is the same as that of exophthalmic goiter (six to one). Clinically, it has been shown by Bence and Engel,[39] van Lier,[40] Carpi[41] and others that the mononuclear leukocytes and lymphocytes are increased in myxedema just as in exophthalmic goiter, and it has long been known that, anatomically, the lymphoid tissue changes are similar in both syndromes. Another observation of interest in this connection is the experience of clinicians generally that the cretin, the exophthalmic goiter or the myxedema patient has lowered resistance toward bacterial infections and Marbé[42] and Fassin[43] have demonstrated a lessening of the alexic activity of the blood-serum in both exophthalmic goiter and myxedema, and also that this lessening is the reverse of what obtains following the administration of iodin or desiccated thyroid. We have already described the anatomical features of the special form of atrophy that supervenes in the marked hyperplasia as myxedema develops and have pointed out that it may often be detected in advance of definite clinical manifestations. The iodin relations which obtain in these special atrophies of cretinism or myxedema are naturally only a continuation of the gradual lessening which characterizes the several degrees of hyperplasia.

It is generally stated that myxedema is the antithesis of exophthalmic goiter. This is based largely on the subjective and symptomatic manifestations and the fact that the manifestations of exophthalmic goiter are most pronounced during the early or developmental stage of the thyroid

32. Hirschl: Wien. klin. Wchnschr., 1900, xiii, 622.
33. Osler: Jour. Nerv. and Ment. Dis., 1899, xxvi, 65.
34. Sollier: Rev. de Méd., 1891, xi, 1000.
35. Jolly: Jour. Am. Med. Assn., 1899, xxxii, 814.
36. Williams: Brit. Med. Jour., 1893, i, 799.
37. Gautier: Rev. méd. de la Suisse Romande, 1898, xviii, 625.
38. Gowan: Lancet, London, 1895, i, 478.
39. Bence and Engel: Wien. klin. Wchnschr., 1908, xxi, 905.
40. Van Lier: Beitr. z. klin. Chir., 1910, lxix, 201.
41. Carpi: Berl. klin. Wchnschr., 1910, xlvii, 2059.
42. Marbé: Compt. rend. Soc. de biol., 1909, lxvii, 362.
43. Fassin: Compt. rend. Soc. de biol., 1909, lxvi, 457.

hyperplasia, while manifestations of myxedema occur during the atrophic stage. The biological or objective phenomena of the physiology, the anatomy and the chemistry of the thyroid in exophthalmic goiter and myxedema, as we have shown, are closely interwoven. The fundamental conception and demonstration of myxedema or cretinism as the result of the lessening of the physiological secretion of the thyroid is the most thoroughly established fact in the pathological physiology of the thyroid. We would emphasize that the essential thyroid disturbance in myxedema is a lessening of the physiological value of the secretion and not necessarily a quantitative lessening, since a majority of all animals from fish to man have or have had enlarged thyroids both in cretinism and in myxedema. To use the words of Morel: "Goiter is one stage on the road to cretinism or myxedema." Morel's dictum might, in the light of recent work, be modified to read: "Active hyperplasia is the first manifestation of thyroid insufficiency," for the reason that we now know that an animal may be cured of any general disturbance of which the goiter is a manifestation and still have an enlarged thyroid (colloid goiter), in the same sense that an animal with rickets may recover, although the bone deformities persist.

Faure[44] has tersely put the kernel of the whole argument as follows: "If myxedema is due to a deficiency, and exophthalmic goiter to an excess of thyroid secretion, then both syndromes could scarcely coexist in the same individual." But it is now known that the two syndromes overlap to a greater or lesser extent in all of the cases of exophthalmic goiter in which the impairment of thyroid function is allowed to continue unchecked.

Horsley[45] has pointed out that nervousness and tremor are quite constant manifestations of the early stage of myxedema and that the reason we do not observe it more often is that the patients present themselves with the disease well advanced. He[46] also described a nervous, excitable stage in the thyroidectomized monkeys preceding the development of the more characteristic symptoms of cachexia strumipriva. Later McGarrison[47] noticed and carefully recorded a nervous stage preceding the classical manifestations of endemic cretinism in the Gilgit and Chitral Districts of India.

We believe that further study will reveal the frequent existence of nervous manifestations of the exophthalmic goiter type during the developmental stage of myxedema, just as anatomical studies have shown that

44. Faure: Presse méd., 1899, ii, 174.
45. Horsley: Brit. Med. Jour., 1885, i, 381.
46. Horsley: Proc. Roy. Med. and Chir. Soc., London, 1886, xl, 6.
47. McGarrison: Proc. Roy. Med. and Chir. Soc., London, 1908, ii, No. 3, Med. Sect., p. 1.

the thyroid tends toward and usually does undergo hyperplasia prior to the development of the myxedema complex.

Loss of scalp and body hair and caries of the teeth are almost constant accompaniments of frank exophthalmic goiter. Pigmentation of the skin, either general or local, is also commonly observed. Many of our most severe cases clinically have shown no wasting of the subcutaneous tissues, while in others the wasting was extreme. We have been led to look on these manifestations as the very earliest and mildest of the series of symptoms which characterize developing myxedema.

In this connection we wish to report the major features of a typical case which we have been allowed to follow through the courtesy of Prof. J. P. Sawyer and Dr. A. N. Dawson, since it embodies the most characteristic events in the course of exophthalmic goiter.

The patient, a girl aged 18, presented herself at Charity Hospital in October, 1908, with all the cardinal symptoms of exophthalmic goiter. She was admitted to the hospital and improved rapidly during the five weeks of rest and general medical treatment. She then returned to her work but relapsed during the following May and was readmitted to Charity Hospital in June, 1909. At this time the right thyroid lobe was removed. The operation was followed by the typical pulse and temperature reaction, the pulse reaching 160 and the temperature 105 degrees. Five weeks after leaving the hospital she was again admitted with typhoid fever. This disease ran an uncomplicated course but was prolonged and during the third week of convalescence it was noticed that the pulse was becoming more rapid and the remaining thyroid lobe was enlarging. She left the hospital in November, 1909, and was not seen until March, 1910, when she presented the following picture: She had gained thirty pounds. The subcutaneous tissues were everywhere thickened. The skin was dry, save for sweating of the palms of the hands and the soles of the feet. There was nearly complete loss of the body and scalp hair and the decay of the teeth had progressed rapidly. The pulse was regular and averaged 120 beats per minute. The remaining thyroid lobe had enlarged until it exceeded the size of the combined lobes before operation. Menstruation had not occurred since the typhoid fever. A diagnosis of supervening myxedema was made and as there was a great excess of very actively hyperplastic thyroid tissue present, iodin in the form of the syrup of the iodid of iron 0.3 c.c. three times daily was given. At the end of two months the remaining thyroid lobe was firm, much reduced in size and had completely involuted to the colloid or resting stage. A new growth of scalp, axillary and pubic hair developed, menstruation began again during the third month and the thickened subcutaneous tissues returned to their normal appearance. The exophthalmic goiter symptom-complex, though somewhat ameliorated, is still present (Dec. 28, 1910), (pulse 110, tremor, exophthalmos and a small firm left thyroid lobe).

This case illustrates the usual way in which myxedema is associated with exophthalmic goiter. It also illustrates that it is possible to relieve the myxedema symptom-complex by the use of iodin alone, if sufficient active thyroid tissue is present, and that by relieving the myxedema and by completely reversing the histological state and iodin content of the thyroid, only slight amelioration of the exophthalmic goiter symptom-complex took place.

8. RELATION OF POSTOPERATIVE MORTALITY TO THE ANATOMICAL CHANGES IN THE THYROID AND LYMPHOID TISSUES AND TO THE IODIN CONTENT OF THE THYROID

Complete data on which to estimate the true postoperative mortality are not available. The published statistics, of which the following are examples, Dunhill,[48] eighty-eight cases with 1.1 per cent. mortality, the Mayos,[49] 405 cases with 4.7 per cent. mortality, Kocher,[50] 494 cases with 3.4 per cent. mortality, Krecke,[51] 108 cases with 9 per cent. mortality, Hale White,[52] eleven cases with 36 per cent. mortality, H. Mackenzie,[53] thirteen cases with 38 per cent. mortality, and Gebele[54] thirty-six cases with 19 per cent. mortality, show greater variations than could likely be attributed to operative skill and at the same time omit those data which are known to be most indicative of the severity of the cases, viz., the histological condition of the thyroid and lymphoid tissues. Mortality statistics based on the total number of cases clinically diagnosed as exophthalmic goiter give no accurate idea of the real mortality (1) because different observers exercise different degrees of liberality in diagnosing exophthalmic goiter, (2) because such statistics convey no idea of the stage or the severity of the disease, and (3) because the collected autopsy reports show that the mortality is greatest in those patients with marked thyroid and lymphoid hyperplasia. Unless the histological condition of the thyroid and the lymphoid tissues, together with the pulse-rate and temperature reactions both before and after operation are given, no estimate of the operative risk and the types of cases subjected to operation can be gained.

We have grouped all cases as postoperative deaths which have died within four days after operation with high temperature and pulse-rates, believing that greater error is introduced in attributing death in these cases to one or another of the many possible accompanying diseases or accidents.

Of the sixty-nine cases included in this study, twelve or 17.4 per cent. died—ten females and two males (see Table 3).

The mortality arranged according to the four major anatomical groups of thyroid changes is as follows: three[55] cases with adenomata with no mortality, five cases with normal or normal-colloid glands with no mor-

48. Dunhill: Brit. Med. Jour., 1909, i, 1222.
49. Mayo, C. H.: Surg., Gynec. and Obst., 1909, viii, 237.
50. Kocher: Brit. Med. Jour., 1910 ii, 931.
51. Krecke: München. med. Wchnschr., 1909, lvi, 15.
52. White, Hale: Quart. Jour. Med., 1910, iv, 89.
53. Mackenzie, H.: Brit. Med. Jour., 1910, ii, 935.
54. Gebele: Beitr. z. klin. Chir., 1910, lxx, 20.
55. The five other cases with adenomata are included under normal-colloid or colloid glands (see Table 3).

tality, eighteen cases with pure colloid goiters with two deaths, or a mortality of 11 per cent., and forty-three cases with active hyperplasia with ten deaths, or a mortality of 23 per cent. It is thus seen that the highest mortality occurs in the group of active hyperplasias and by arranging the ten fatal cases of this group according to the degree of active hyperplasia present, it is found that all were associated with advanced degrees of active hyperplasia.

The symptoms, as we are at present able to interpret them, offer inconstant and unreliable criteria of severity and risk of operation except in those cases with manifestations of supervening myxedema, which are the greatest operative risks. Three of our four patients died following operation. Thus, it may be stated at present that the thyroid and lymphoid hyperplasia offer the most constant criteria of severity and that the mortality varies with the degree of hyperplasia of these tissues.

Concerning the relation of mortality to the iodin content, there is no literature bearing directly on this feature, although it could be inferred that since the mortality is greatest in those cases with marked hyperplasia, and since iodin normally varies inversely with the degree of hyperplasia, that the mortality would be highest in those cases with low iodin content. The accompanying tabulation of nine[56] of the fatal cases bears out this inference (see Fig. 9).

There are three general hypotheses as to the cause of the phenomena of high pulse-rates, high temperatures and death in these cases: (1) that they are the result of squeezing an excess of thyroid secretion into the organism from gland manipulation at operation; (2) that they are the result of status lymphaticus; (3) that they are the result of the general state of exhaustion and weakness of the organism.

Taking up the first hypothesis, Putnam[57] suggested it in order to explain the phenomena on the basis of a hyperthyroidization theory. It is still widely held by those who think both the temperature and pulse reactions are the result of a hyperthyroidization, but there is now sufficient evidence to render it untenable, first because the operative mortality is greatest in those patients with small, cirrhotic glands and low iodin content, and is least in those patients with excessive thyroid tissue and high iodin content. This is the opposite of what should obtain if the secretion caused the symptoms and iodin determined the secretion's major activity. Second, the gravest risks are those patients with symptoms of

56. Three fatal cases (Cases 269, 381 and 265) have been excluded because iodin was administered for too short an interval before operation for corresponding histological changes to occur. Thus, the iodin contents were 4.02, 1.31 and 1.15 mgm. per gram of dried gland, while the histological diagnosis in these cases was colloid-moderate hyperplasia, and experience has shown that such iodin contents can coexist with such degrees of active hyperplasia only in cases in which insufficient time has elapsed since the administration of iodin began.

57. Putnam: Brain, 1894, xvii, 214.

myxedema supervening on the exophthalmic goiter syndrome. Third, these phenomena of high temperature, high pulse-rate and death occur as well after arterial ligation as after lobectomy. Fourth, operations elsewhere on the body or trauma or shock are, with proportionate frequency, followed by these phenomena. Thus, Crile[58] has reported a patient dying after ether anesthesia alone and cites a patient dying from the shock

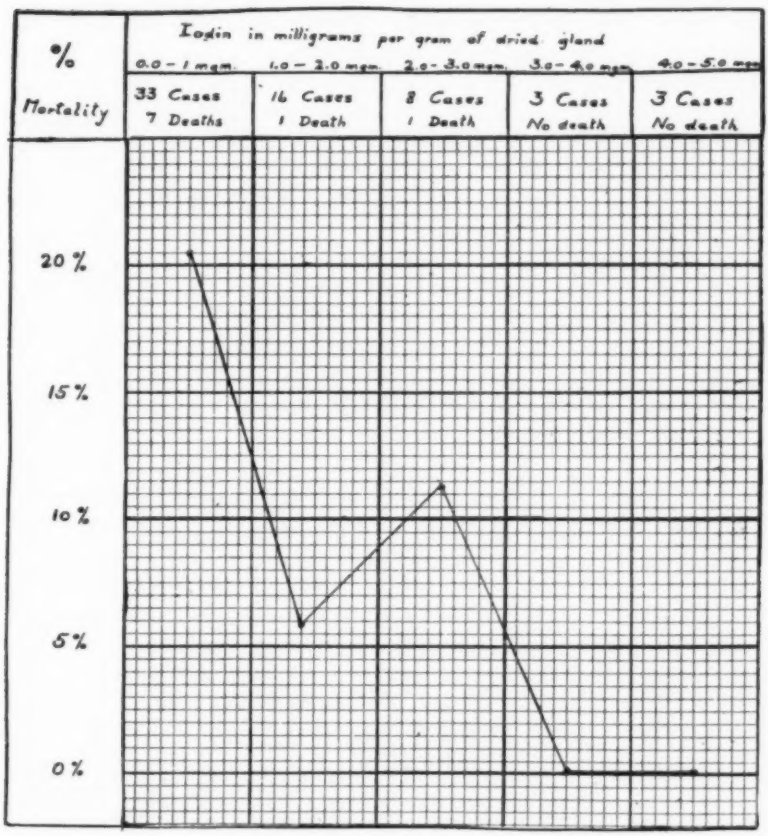

Fig. 9.—Mortality and iodin content.

incident to a fracture of the femur. Hirst[59] has collected seventy-one operations other than thyroid in cases of exophthalmic goiter in which the same phenomena of high pulse and temperature were present, of which fifteen terminated fatally. Fifth, a comparison of the postoperative rise of

58. Crile: Ohio State Med. Jour., 1907, iii, 293.
59. Hirst: Am. Jour. of Obst., 1905, lii, 367.

the temperature and pulse in our group of fatal cases with a group of non-fatal cases of similar thyroid and lymphoid changes shows that the manifestations differ only in degree (Figs. 7 and 8).

The second view, that the lymphoid hyperplasia of the thymus, spleen and lymph glands is the cause of death in these cases has been discussed by Capelle, Caro, Boit and others. Most of the fatal cases, as has been shown by all observers, have lymphoid hyperplasia. The studies of Sawyer, Kocher, van Lier, Carpi and others have shown that this lymphoid hyperplasia, while in no sense specific for the fatal cases or, indeed, for exophthalmic goiter in general, is present to some degree during the progressive stage of true exophthalmic goiter whether ending fatally or not.

The third view, that death is the result of the failure to compensate for some general nutritional disturbance seems the more probable. This failure of compensation is manifested objectively by the series of morphological changes easily demonstrable in the thyroid and lymphoid tissues and which perhaps also exist in other tissues whose objective manifestations of the compensatory reaction are less easily detected. The interpretation of these cell changes as indicative of cell exhaustion is based on the well-known experiments of R. Hertwig and his pupils[60] in producing similar morphological changes in protozoon cells by overwork, overfeeding or starvation, and on the morphological studies in tumor cells by Professor Howard and Dr. Schultz.[61]

The study of the series of changes which take place in a thyroid as it passes from the normal gland through active hyperplasia to the end stage of cretinoid or myxedematoid atrophy, forces us to interpret this process as one of compensation to meet increased functional demands and the failure of this compensation leads to a gradual loss of the finer cell nutrition and, in consequence, of the finer cell function. One cannot say that the general loss of cell energy and of the ability of the body-cells to regulate their function—the two most characteristic features of the disease—are or are not due to a poison. There is, however, no objective evidence that either the thyroid or lymphoid tissue is producing such a poison, but rather the evidence would seem to indicate that if a poison does exist, these tissues are attempting to control it.

9. TREATMENT OF EXOPHTHALMIC GOITER

A correct estimation of the value of any plan of treatment is easy or difficult in proportion to the closeness with which the disease follows a type. If the disease is acute and typical, the therapeutic value of any measure is readily determined; but if, on the contrary, the course of the

60. Arch. f. Protistenk. (Suppl.) Festband f. R. Herting, 1907.
61. Schultz: Jour. Exper. Med., Suppl. No. 1911.

disease is chronic and subject to many spontaneous remissions and exacerbations it is extremely difficult to reach a just estimate of the value of any plan of treatment. And when in addition the pathological processes cannot be sharply separated from the physiological, the difficulties opposed to correct judgment are further increased. There is no disease the history of which better demonstrates the truth of these principles than does exophthalmic goiter.

General suggestions covering the recognized facts in the pathology and the physiology of the disease only can be attempted, because in so protean a disease, and in a disease which so markedly tends toward spontaneous recovery, false judgments as to the success or failure of a given measure are unavoidable. The details of application of the general principles to be outlined must be left to the good judgment of the physician and there is perhaps no disease in which the adaptation of the physician's suggestions to the individual case is more important for the obtaining of satisfactory results.

The prevailing modes of treatment have followed closely the prevailing theories as to the causation of the disease. The therapeutic measures at present employed may be divided into two groups, as follows:

1. Those directed toward the correction of metabolic disturbances, and in particular the nervous exhaustion.

2. Those directed toward reducing or counteracting the thyroid secretion.

Beginning with Group 1, the first requisite is a carefully taken history to ascertain the underlying factors in the central nervous-system exhaustion, whether it can be traced to worry, care, anxiety, fright, overwork, strain; infectious diseases, as typhoid fever, rheumatism or influenza; gastro-intestinal disturbances or any of the many other disturbances with which the symptom-complex may be associated.

Rest, both mental and physical, stands first in importance among all the beneficial measures now at our command. Those who have had the most favorable results with surgical measures have used prolonged rest both before and after operation. As nearly absolute mental rest as possible should be striven for. This may be attempted by a variety of means, but again the physician must adapt his method to suit the tastes, surroundings, means, etc., of the patient. Rarely can one obtain rest at home. More successful is a change of environment, in a hospital or a sanitarium or in the country. In severe cases a rigid Weir Mitchell treatment may be necessary. In milder cases the diversion of a leisurely voyage, or a sojourn at some quiet place by the sea or in the highlands, or a protracted visit with a distant relative or a leisurely-taken camping trip may open up other avenues of mental activity which are as rest-producing to the nervous mechanism as physical rest is to the muscle-cell.

Mental rest frequently has little association with physical rest and we often fall into the error of attempting to obtain mental rest by the same methods that are commonly employed to induce physical rest. The great object to be attained in all cases is to get the patients to a place where they can enjoy quiet, away from their cares, imaginary or real, away from their social duties and their work.

Baths have an important place in the treatment, both for their sedative and their tonic effects. A course of daily baths with carefully graduated temperatures should be instituted. In the severe, maniacal or restless cases the hot bath (100 F.) each evening usually ensures sleep and rest. As the patients improve, or in milder cases, the temperature may be graduated downward, thus passing from the sedative to the mildly tonic effect. Perhaps in no case is it wise to reduce the bath temperature below that which is necessary to induce mild vasoconstriction.

Exercise: There are three forms: (1) active (voluntary) movements, (2) passive movements and (3) electricity. In all severe cases the muscular weakness precludes attempts at active exercise, but massage should be instituted in connection with the hot baths. In improving or mild cases active exercise as walking, mild gymnastics, etc., should be instituted. These exercises should be graduated so as to avoid fatigue and at the same time to take advantage of the patient's increasing endurance. Electricity has been extensively used, and undoubtedly many of the symptoms have subsided under its use, but the fact that there is no agreement among observers as to the kind or strength of current to use—some recommending the static, others the high frequency, some the galvanic, others the faradic—has led to the conclusion that whatever benefit is obtained is largely due to the mental impression on the patient and the muscular movements induced.

Concerning climate great differences of opinion exist. Some insist on residence in the mountains, others at the seashore. All we know may be summed up by saying that since these patients withstand heat badly, one should avoid the hot, humid climates and seek a cool, dry, pure atmosphere. In patients with cardiac weakness the altitudes may be harmful. In general, mountainous regions of moderate elevation (1,000 to 5,000 feet) are the most favorable and offer less monotony than level surroundings.

Diet: Patients often crave unsuitable articles of food, as pickles, spices, pastries, candies, nuts, etc. The food should be plain, well cooked, wholesome, and taken at regular intervals. Stimulants should be avoided. The fact that these patients usually retain good appetites cannot be overlooked when weighing the symptomatology of the disease. It may possibly be interpreted as the organism's attempt to repair the tissue waste. And since tissue waste is one of the manifestations of the disease, we believe

that the diet of these patients should not be curtailed as to proteins, fats or carbohydrates, and that none of the usual articles of food (meats, milk, eggs, butter, sugars, starches, fruits and vegetables) need be restricted except as special indications arise in the individual cases, as for instance glycosuria, diarrhea, vomiting, etc.

Suggestion: The value of suggestion in exophthalmic goiter is universally recognized. The psychical condition of these patients is very unstable. Trivial incidents may encourage them and equally trivial happenings may depress them. It is necessary to acquire the confidence of the patient when time is such an element in the treatment, and only in this way can we expect cooperation. The physician should encourage and cheer the patient. In most cases this can be done without resort to strategy, not to speak of quackery. Hypnotic suggestion should be condemned.

Drugs have little actual value. Speaking of the almost endless list as a whole, their beneficial influence is determined largely by the mental impression on the patient and by the skill and intelligence with which their use is adapted to each particular case. The general hygienic measures instituted at the same time are often underestimated. It should be pointed out that the limits of safety in the use of drugs are very narrow in this disease and drugs should, therefore, be used in small doses and under careful control. The use of drugs is largely symptomatic and may be grouped as follows:

1. The cardiovascular group includes digitalis and its derivatives, strophanthus, convallaria, strychnin, ergot, atropin, veratrum viride, aconite, nitrites, etc. The heart and vessels need neither stimulation nor depression. They need regulation. This regulatory control can be regained but slowly under any condition. Digitalis is the most commonly used. Its use should be confined to such conditions as acute dilatation, valvular lesions or actual myocardial disease. It should not be used for the tachycardia. Rest in bed and the ice-bag are safer and better.

2. For the symptoms of nervousness, restlessness and insomnia a large list of drugs has been used. Among the more prominent drugs are opiates, bromids and coal-tar products. Since the above symptoms are probably due to a loss of, or a weakened inhibitory control over, the body functions, it is not rational therapy to offset this by correspondingly depressing the accelerator mechanisms. The end to be attained is to assist the organism in regaining this regulatory control, and rest in quiet, congenial, comfortable surroundings, warm baths, etc., are more important than drugs. An occasional dram dose of sodium bromid before retiring may be useful if the above measures are impracticable. These patients are peculiarly susceptible to opium and it should not be used. The same is true of the powerful hypnotics and depressants.

3. Iron, arsenic, sodium phosphate and quinin hydrobromate have their advocates. Since the treatment of every case must be carried out on general principles and complications as dyspepsia, diarrhea, constipation, vomiting, anemia, etc., dealt with as they arise, these drugs as well as many others are often of value in individual cases.

4. The use of such animal extracts as thymus, adrenal, ovary, testis, spleen, pituitary or brain tissue is purely empirical and has no known influence. With desiccated thyroid it is different. According to the hyperthyroidization theory it should make the cases worse, while according to the hypo- or dys-thyroidization theory it should produce improvement. The majority of the reports indicate that the drug in small doses makes the patients clinically worse. Nevertheless, there are large numbers of cases in which no noticeable effect has been produced by the drug even in large doses. There are also numerous cases in which definite improvemet has followed its use. Several known factors have helped to bring about this lack of uniformity of results. (1) The activity of desiccated thyroid is determined by the iodin in organic combination, and in commercial preparations this is quite variable (the causes for this variation have been discussed in an earlier paper by Marine and Williams[62] and by Hunt and Seidell.[63] (2) The doses used have usually been those arbitrarily established for goiter in general. (3) Clinically, exophthalmic goiter includes a very broad group of cases as regards the duration, prominence, severity and character of the symptoms.

It is certain, however, that desiccated thyroid induces the same anatomical changes in the exophthalmic goiter as in any other developing goiter and that these changes are identical with those produced by iodin, viz., (a) an involution to the colloid state, (b) an increase in the iodin content and (c) a decrease in the blood-supply. In the so-called secondary exophthalmic goiter cases and in cases with manifestations of developing myxedema, doses of from 2 to 5 gr. (0.12 to 0.3) daily of the commercial thyroid are often beneficial. In the acute, severe, primary exophthalmic goiter cases this drug should not be employed unless one uses a purified iodothyreoglobulin hypodermatically in doses of $^1/_{50}$ gr. (0.0012) as recommended by Beebe.[64] On the whole this is a dangerous drug and should be used only in its purified and standardized form in cases under the closest observation. We feel certain, however, that its use in this disease will become more general when the above conditions are fulfilled.

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62. Marine and Williams: The Relation of Iodin to the Structure of the Thyroid Gland, THE ARCHIVES INT. MED., 1908, i, 349.

63. Hunt and Seidell: Commercial Thyroid Preparations . . ., Jour. Am. Med. Assn., 1908, li, 1385.

64. Beebe: Treatment of Thyroidism by Specific Serum, THE ARCHIVES INT. MED., 1908, ii, 315.

5. Iodin has much the same action in exophthalmic goiter with active thyroid hyperplasia as has iodothyreoglobulin, and in addition has the advantage that the dose can be controlled and that the reaction produced depends on the size of the dose and on the existing degree of the thyroid hyperplasia. We have carefully followed the use of iodin in seventeen cases and have not seen any of the injurious effects commonly described.[65] Iodin should be administered by mouth and preferably in the form of the syrup of the iodid of iron, syrup of hydriodic acid or sodium iodid. The initial dose should be small. In extreme cases we have used the syrup of ferrous iodid in doses of 5 minims (0.3 c.c.) daily for the first week, 5 minims (0.3 c.c.) twice daily for the second week and 10 minims (0.6 c.c.) twice daily for the third week. In mild cases the initial dose may be 5 (0.3) or even 10 (0.6 c.c.) minims twice daily.

Group 2 includes those measures directed toward reducing or counteracting a theoretical hypersecretion. The experimental basis for this theory of the nature of the disease is becoming exceedingly frail.

A. Surgical measures rank first. The more important ones are partial extirpation of the gland, arterial ligation, stretching or excision of the cervical sympathetic, and various combinations of these. It is extremely difficult to arrive at any accurate estimation of the value *per se* of any of these measures. No two observers exercise the same liberality or restriction in making the diagnosis. Successes are more often reported than failures. The general hygienic and nutritional treatment instituted before and continuing for a long time after operations have not been taken into account. Internists generally have used a more rigid standard of cure than have surgeons. The statistics of mortality, improvement and cure based on the total number of cases clinically diagnosed are, for the above reasons, of little value. We have followed a large group of cases from the clinic of Dr. Crile and our findings agree with those of Wilson,[66] Capelle and others that the severity and mortality statistics are more accurately computed from the actual thyroid and lymphoid reactions than from the clinical picture. Indeed, we would go further and state with Crile[67] that it is impossible at present to state accurately the net clinical results of any operative procedure. None of the operative measures or their modifications has been followed by uniform results. As Mackenzie[68] points out, surgical measures most often fail in those cases in which medical treatment most often fails and particularly in those cases which

65. Kocher (Arch. f. klin. Chir., 1910, xcii, 1166) has recently set forth at length the untoward effects of iodin in exophthalmic goiter. We believe such effects are due to the abuse and not to the physiological use of the drug.

66. Wilson: Am. Jour. Med. Sc., 1908, cxxxvi, 851.

67. Crile: Post-operative Results in Exophthalmic Goiter and Tumors, Jour. Am. Med. Assn., 1909, liii, 1675.

68. Mackenzie: Allbutt's System of Med., 1908, iv, pt. 1, 383.

theoretically should be most improved. It is impossible to tell whether ligation of one, two or three thyroid arteries will be followed by improvement or not. So also with partial extirpation; improvement may or may not follow removal of one-fourth, one-half or three-fourths of the gland. So also with the sympathetic operation, either stretching or resection may or may not be followed by improvement. Whatever thyroid operation is made, the other factors being constant, the postoperative reaction (so-called hyperthyroidism) and the operative mortality are, in general, proportional to the degree of active thyroid and lymphoid hyperplasia (the anatomical indices of severity). Also many authors have shown that operations on other parts of the body, or injuries, as a fractured leg, or mental shocks, are followed by the temperature and pulse reactions and sometimes death, in proportion to the anatomical severity of the disease.

It is the general experience that a larger percentage of improvement follows in those cases in which some operative measure has been carried out than in those treated medically, but as Bier[69] points out, it is largely subjective during their stay in the hospital and the objective signs clear up only after prolonged treatment. None of the surgical explanations thus far offered for the apparent improvement is free from weighty objections. In our opinion operations should not be undertaken until the thyroid has returned to its colloid or resting state, whether this has occurred spontaneously during general treatment or has been hastened by the action of minute doses of iodin. What has been said refers only to operative measures applied expressly for the relief of the symptoms of the exophthalmic goiter. In each case the general indications for operation, as (1) the relief of mechanical pressure effects, (2) correcting deformity, (3) thyroid tumors and (4) psychic effects, should be considered.

B. The chief non-surgical measures in use to counteract or reduce the hypothetical thyroid hypersecretion are (1) the antithyroid serum of Moebius, (2) the milk of thyroidectomized goats, (3) the thyreolytic serum of Beebe and Rogers, and (4) the Roentgen rays. The hypothetical action of Moebius' serum and of the milk of thyroidectomized goats is one of neutralization. It rests on the assumptions (1) that the serum or milk of thyroidectomized sheep and goats contains an accumulation of substances which the thyroid secretion would normally neutralize and (2) that the gland of exophthalmic goiter is producing an excess of secretion. As with all other remedies some observers report beneficial, others negative results. The prevailing opinions are (von Strümpell, Eulenberg, Erb and Eichhorst[70]) that any improvement occurring during their use is not greater than could be ascribed to rest, hygiene and the passage of time.

69. Bier: Med. Klin., 1908, iv, 16.
70. Med. Klin., 1908, iv, 39.

Certainly no specific action has been demonstrated. The theory of action of Beebe and Rogers' serum is that it inhibits the action of the thyroid cells or destroys them. The serum is made by injecting into rabbits or sheep the nucleoproteins of human thyroid. They claim for the serum a high degree of specificity. The work has not been confirmed.[71] Our experience with its therapeutic use is confined to fourteen cases. No improvement could be made out above what normally occurs with rest in bed. We were able to examine the thyroid glands histologically from three of the cases (in two cases during and one about four weeks after treatment) but could not detect any lytic action on the thyroid epithelium.

Roentgen rays have also been used to inhibit or depress the gland's activity. In some cases the gland becomes smaller. No definite thyroid changes are recorded beyond an increase of the capsular and pericapsular fibrous tissues. The value of this form of treatment is still problematical.

10. SUMMARY AND CONCLUSIONS

The anatomical changes in the several body tissues in exophthalmic goiter are variable and manifold. The most prominent and most constant change is active hyperplasia of the thyroid and lymphoid tissues. These changes are not constant, since the exophthalmic goiter syndrome, as at present recognized, may coexist with a normal thyroid, with a colloid goiter, with an actively hyperplastic thyroid, with an atrophic thyroid or with a tumor of the thyroid.

The great majority of individuals presenting this syndrome in recognizable form have some degree of active thyroid and lymphoid hyperplasia, and we believe that all true cases with complete clinical syndromes have had, during their developmental stage, active thyroid and lymphoid hyperplasia.

Active thyroid and lymphoid hyperplasia are not specific for this syndrome, since similar anatomical changes are present in a variety of other abnormal body states.

The series of anatomical changes which occur in a thyroid as it passes from its normal or its colloid state through active hyperplasia and on to atrophy or to colloid goiter represents this tissue's biological reaction whenever those biochemical disturbances in the organism's nutrition occur which excite its compensatory activity.

Active thyroid hyperplasia means thyroid insufficiency, and although the causes which excite this activity are unknown and, therefore, may or may not be multiple, still, the basic anatomical reaction of the thyroid tissue seems to be the same in all the several clinical varieties of goiter and, indeed, seems to be the only one with which the thyroid tissue is

71. Taylor, A. E.: The Treatment of Exophthalmic Goiter with Specific Antiserum, Jour. Am. Med. Assn., 1911, lvi, 263.

endowed. The only defined physiological activity of the thyroid secretion is that determined by its iodin content. Iodin is related to the exophthalmic goiter thyroid in the same way that iodin is related to the thyroid of other clinical associations and of other animals as well, viz., that iodin varies inversely with the degree of active hyperplasia. The ability of the exophthalmic goiter thyroid to take up iodin varies with the degree of active hyperplasia (hence inversely with the amount of iodin present) and is similar to that of other active thyroid hyperplasias in man and the lower animals. Iodin induces the same series of anatomical changes in exophthalmic thyroid goiter as in the other varieties of thyroid hyperplasias in man and animals.

The temperature and pulse reactions both before and after operation tend to vary with the degree of thyroid and lymphoid hyperplasia. The differences between the reactions in cases with normal or with colloid glands and the reactions in cases with marked hyperplasias are too slight for a suggestion of any cause and effect relation. The pulse and temperature reactions and the thyroid hyperplasia are parallel and resultant phenomena dependent on more general and more remote causes.

An incomplete exophthalmic goiter syndrome may exist with the thyroid normal, or the thyroid may be markedly hyperplastic with the syndrome absent, or, finally, the histological structure and iodin content of the thyroid in a given case of exophthalmic goiter may be reversed without necessarily modifying the symptom-complex.

Myxedema does not precede; it occasionally accompanies, but usually supervenes late in the course of exophthalmic goiter and is to be looked on as the end stage of thyroid insufficiency.

The immediate postoperative mortality with its associated high temperature and pulse-rate in uncomplicated cases, varies with the degree of active lymphoid and thyroid hyperplasias and is most probably the result of the organism's profound general weakness and exhaustion. The degree of active lymphoid and thyroid hyperplasia is therefore the best index of the severity of the disease.

The essential physiological disturbance of the thyroid in exophthalmic goiter is insufficiency, its reaction compensatory and its significance symptomatic.

NOTE.—We wish to acknowledge our indebtedness to Professor G. N. Stewart for many criticisms and suggestions, and to Professor G. W. Crile for the use of his surgical material.

THE SYMPTOMATOLOGY OF TEMPOROSPHENOIDAL TUMORS*

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INTRODUCTION

In a paper on the "Localization of Intracranial Tumors," Byrom Bramwell[1] has stated that in two cases reported by him in which the tumor involved the temporosphenoidal lobe, there were, practically speaking, no localizing symptoms:

> I have been in the habit of regarding the temporosphenoidal lobe as, par excellence, *the* silent area of the brain. In the relative order with which they can be most easily and certainly diagnosed . . . I would place tumors in the following situations: (1 and 2) pons Varolii and medulla oblongata; (3) centrum ovale (cases in which the optic radiations of Gratiolet are directly implicated); (4) tumors of the occipital lobe, involving the half-vision center or the optic radiations; (5) tumors of the motor area, in which the tumor produces irritation and gives rise to localized epileptiform convulsions; (6) tumors of the cerebellum; (7) tumors of the frontal lobe; (8) tumors of the upper part of the parietal lobe; *and last of all, the most difficult to diagnose and locate,* (9) *tumors of the temporosphenoidal lobe* and especially, of course, tumors of the right temporosphenoidal lobe.

That the words which I have underlined represent an opinion very generally held is evident, when we find that writers of the eminence of Beevor[2] and Mills[3] have also in recent years laid stress on the great difficulty in the diagnosis of tumors involving the cerebral area below the Sylvian fissure.

As an example of this difficulty may be mentioned the case reported by Alexander Bruce,[4] which, notwithstanding the presence of intense headache, right facial weakness and marked disability in speech, was diagnosed as "hysteria," but which on autopsy was found to have a tumor the size of a hen's egg in the anterior third of the left temporosphenoidal lobe.

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*The author wishes to express his thanks and his great indebtedness to the members of the medical and surgical staff of the National Hospital, London, for their permission to make use of the material on which this paper is based.

1. Bramwell, Byrom: Localization of Intracranial Tumors, Brain, 1899, xxii, 37.

2. Beevor: Localization of Cerebral Tumors, Lettsom Lecture, Lancet, 1907, i, 495.

3. Mills: Tumors of the Cerebrum, 1906, p. 36.

4. Bruce: Tr. Med.-Chir. Soc., Edinburgh, 1882, ii, 94.

The consensus of authoritative opinion seems then to characterize the temporosphenoidal lobes as by far the most latent area of the brain. They are vast regions, practically uncharted, for in them experimental physiology has been able to assign definite functions to but comparatively small portions. Again, temporosphenoidal tumors are relatively rare, and observers have only exceptionally been able to study more than single isolated cases. Hence, a systematic examination of the symptomatology of this condition has hitherto been impossible.

During my residence at the National Hospital for the Paralyzed and Epileptic, I had opportunities for repeated examinations of a large number of such cases.

In some, in which the symptoms were clear and the diagnosis certain, the patients, for various reasons, were discharged from the hospital without operation; in others, death supervened and permission for autopsy was refused, in others, again, the growth was found to involve not only the temporal but also the frontal, or parietal or occipital regions, thus possibly introducing doubt as to the causation of the symptoms.

For the purposes of this paper all such cases have been neglected, and only those nine in which the lesion was proved to be confined to the temporal lobes will be reviewed. By thus rigorously confining my attention to indubitable cases of temporosphenoidal tumor, I hope convincingly to demonstrate, first, that such tumors present a definite and uniform symptom-complex, pathognomonic of tumors in this region and in this region alone; and, second, that not only can they with certainty be diagnosed, but that it is still further possible clinically to distinguish those in the right hemisphere from those in the left.

It must be remembered that an intracranial tumor is not merely a localized lesion affecting centers in its immediate vicinity alone, but it also acts as a foreign body growing in a non-distensile space and producing in a definite and almost invariable sequence, compression of centers more or less remote.

The symptoms-complex to be put forward later as characteristic of tumors in the right and in the left temporal lobes, are the result of systematic examinations of patients with especial regard to the effects of irritation or destruction of centers proved experimentally to be situated in these areas, and also to the results of compression in all directions on adjacent structures; as will be shown, the success attendant on the subsequent surgical procedures has been considerable.

It may be said that the greater the latency of a brain area, the greater the difficulty in the diagnosis of damage to that area, but also, if accessibility be granted, the more safely can one operate on that area.

The value of the removal of any intracranial growth as regards the restoration of normal health to the patient must depend largely on the

degree of latency of the brain tissue affected, and the ability of the patient to carry on a useful or comfortable existence without the aid of that brain area; the removal of a left-sided subcortical fronto-parietal growth resulting, perhaps, in complete right hemiplegia and motor aphasia, is an enterprise not lightly to be undertaken; nor is a tumor in one of the pontine angles in a much more favorable position, in spite of the power of the unaffected lobe of the cerebellum to effect more or less compensation for the destruction of its fellow; but in the right temporo-sphenoidal lobe we have a region comparatively latent and eminently accessible.

THE LOCALIZATION OF THE CENTERS FOR HEARING

By extirpation of the posterior divisions of the three external temporal convolutions of each hemisphere, Munk[5] was able to produce complete deafness in dogs: by varying the area of cortex removed, he believed that he could distinguish separate centers concerned with "cortical" and "psychic" hearing, and also with the exact appreciation of pitch; the higher tones apparently were perceived in the anterior, and the lower in the posterior parts of these convolutions.

His views were not endorsed by Ferrier,[6] whose experiments showed that in monkeys complete deafness followed the cauterization of the superior temporal convolutions on both sides of the brain.

The effect of stimulating the superior temporal convolution of one side was found by Ferrier,[6] Hitzig[7] and Goltz[7] to consist in a pricking of the opposite ear, wide opening of the eyes, dilatation of the pupils and turning the head and eyes to the opposite side: all the secondary phenomena of audition.

On the other hand, Schäfer,[8] repeating Ferrier's experiments, was unable to obtain the same results.

Campbell[9] found that the temporal convolutions known as the transverse gyri of Heschl differ from all other parts of the temporal lobe in the histological structure of their fibers, which are corticipetal and evidently represent the uppermost link in the chain of auditory neurones.

Having reviewed the functions of the analogues of these fibers in the visual area, Campbell[10] suggests that the transverse temporal gyri represent the primary center for the reception of auditory stimuli; it follows that ablation of these convolutions from both hemispheres would result

5. Munk: Ueber die Funktionen der Grosshirnrinde, 1890, p. 31.
6. Ferrier: Functions of the Brain, 1886, p. 305.
7. Hitzig and Goltz: Quoted by Lewandowsky in Die Funktionen des zentralen Nervensystems, Berlin, 1907.
8. Schäfer: Brain, 1888, xi, 143.
9. Campbell: Histological Studies on the Localization of Cerebral Function, 1905, p. 169.
10. Campbell: Histological Studies . . ., 1905, p. 161.

in total deafness, and there are reasons for believing that the discrepancy between the results of Ferrier's and Schäfer's experiments may have an explanation in the failure of the latter to remove these transverse convolutions.

To summarize this greatly curtailed account, it may be said that the consensus of opinion—experimental, clinico-pathological, and anatomical—is in favor of the centers for hearing being situated in the transverse temporal gyri of Heschl and the posterior three-fifths of the superior temporal convolutions.

THE LOCALIZATION OF THE CENTERS FOR SMELL AND TASTE

Broca[11] in 1879, and Zuckerkandl[12] some years later, demonstrated that in animals with a highly developed sense of smell, there is a corresponding enlargement in the lobus pyriformis, which forms a large part of the hippocampal convolution; it was also shown that the size of the pyriform lobule is greatly reduced in anosmatic animals, and degeneration has been found in this same area after division of the olfactory bulb of the same side.

The presence or absence of the olfactory sense in the lower animals is difficult to determine, but Ferrier[13] found that electrical irritation of the hippocampal lobule in the monkey, cat, dog, and rabbit, was followed by the same reaction in all—a peculiar torsion of the lip and nostril, particularly of the same side; and ablation of this region was followed by a loss of perception of odors and tastes.

Clinicopathological evidence in the main confirms Ferrier's view that the olfactory and probably gustatory centers are situated in the hippocampal lobule, while Hill's[14] observation that the gyrus dentatus of the cornu ammonis is the only structure wholly wanting in the anosmatic brain, tends more accurately to define this localization.

SYMPTOMATOLOGY

The various phenomena of intracranial tumors are usually separated into those produced by general pressure, and those produced by focal disturbance in the neighborhood of the growth. This division is one which many times has been shown to be not only unscientific but also clinically fallacious. In the description of a series of cases having many points in common, however, it is convenient, and solely for this reason is it here retained.

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11. Broca, P.: Localisations cérébrales; recherches sur les centres olfactifs, Rev. d'anthrop., Paris, 1879, ii, 390.
12. Zuckerkandl: Ueber das Riechcentrum, Stuttgart, 1887.
13. Ferrier: Functions of the Brain, p. 316.
14. Hill: The Hippocampus, Phil. Tr. Roy. Soc. London, 1893, clxxxiv.

A detailed examination of the symptomatology of the nine cases under review will enable us to ascertain the characteristic effects of tumor growth in the temporosphenoidal lobes, and later to differentiate those on the right (Cases 1, 2, 3, 4) from those on the left (Cases 5, 6, 7, 8, 9).

Signs and symptoms of general intracranial pressure:

Headache

Headache was present in all. It was rarely constant. It occurred at irregular and often at long intervals, and was usually spoken of as coming in bouts or attacks synchronous in many cases with nausea and vomiting. In only one respect, however, was it of uniform character—as regards localizing value it was little more than useless. In no instance was the pain referred to the temporal region, and only in Cases 1, 4 and 5, was it more frequently felt on the same side as the tumor. In two cases the headache was occipital, in five frontal, and in two it was referred to both the frontal and occipital regions.

It is impossible from a series of nine cases of tumor affecting a single brain area to draw conclusions applicable to other intracranial growths, but it is essential here to emphasize that not in a single instance was the headache of these temporosphenoidal cases referred to the regions of the tumor site. Neither was there in any case localized cranial tenderness.

Vomiting

Vomiting occurred with variable frequency in each of the nine cases; two patients suffered from single attacks of short duration; three had bouts at intervals of several months, and four were subject to attacks at frequent but irregular periods. In all, nausea alone often occurred, and it invariably accompanied the vomiting which in no sense presented features distinguishing it from that of gastric origin: thus, it did not conform to the "projectile type," which by many is erroneously considered to be the essential characteristic of the vomiting of cases of intracranial growth. In four of these cases, nausea and vomiting were particularly associated with subjective unpleasant sensations of taste and smell, and, it might be argued that these features tended to prevent the appearance of the vomiting of classical type, but, broadly speaking, the condition found in this series, is identical with that which occurs in most cases of tumor situated above the tentorium cerebelli.

Papilledema

Leslie Paton[15] recently brought forward statistical evidence to show the impossibility of reaching trustworthy conclusions as to the site of a tumor in the cranial cavity from the greater degree of edema in one or

15. Paton, Leslie: Tr. Ophth. Soc. U. Kingdom, 1908, xxviii, 112.

other of the optic disks. This iconoclastic opinion was at the time emphatically opposed by Sir Victor Horsley and Sir William Gowers, and their view has lately been endorsed by Risien Russell.[16]

Hence it may be of interest to ascertain what diagnostic value this sign possessed in the present series. Bilateral papilledema was present in eight of my nine cases when first they came under observation; in the other, the condition developed within ten days of admission in the eye ipsolateral with the neoplasm, and was found in the contralateral eye also some three or four days later.

In one case (No. 2) the condition was subsiding into atrophy in both eyes, especially the right, but in the remaining eight the type of papilledema was that usually associated with rapid onset and severe intracranial pressure. Careful measurements of the degree of the swelling of the disks were taken in seven cases and were found to vary between three and ten diopters; the greater swelling was ipsolateral with the tumor in five cases and contralateral in one; in the last the edema was equal on either side. It must be again pointed out, with reference to the interpretation of these figures, that the only case in which a greater degree of swelling was found on the side contralateral to the tumor was also the only case in which the pathological process was in a retrograde condition, and that, accordingly, the true meaning of the appearances was that the ipsolateral edema was of earlier origin than the contralateral, had advanced further, and at the time of observation had more nearly completed its life-history: that this is the explanation of the condition will be at once apparent when it is added that in the ipsolateral eye there was much old exudate, whereas in the contralateral there was none; that the retinal arteries were much more diminished in size in the ipsolateral eye, and that the acuity of vision in each eye was in direct proportion to the degree of arterial change.

Sir Victor Horsley[17] has many times pointed out the error of estimating the severity of papilledema by the height of the disk swelling alone and has demonstrated the absolute necessity of considering as one complete picture all the appearances shown by ophthalmoscopic examination before accurate conclusions are to be attained.

It is convenient here to group retinal hemorrhages, retinal striations and the phenomena known as macular figures under the heading of "exudates," and it is generally agreed that in the majority of cases the presence or absence of such exudates assists an observer to an opinion on the severity of the condition.[18]

16. Russell, Risien: The Cerebellum and Its Affections, Lettsom Lecture, Brit. Med. Jour., 1910, p. 497.
17. Horsley, Sir Victor: Brit. Med. Jour., 1910.
18. Gunn, Marcus: Brit. Med. Jour., 1907, p. 1126.

Six of these cases had more exudate on the fundus oculi ipsolateral with the tumor, one had more on the contralateral fundus, and in two cases the amount seemed identical on the two sides. The result of craniectomy on the condition of the optic disks was remarkable; six patients were discharged from the hospital, from four of whom a tumor had been removed. In two of these papilledema had disappeared a month after the operation and in each of the other two it had subsided by four diopters; this result was associated in every case with marked improvement in visual acuity.

In the two cases in which the tumor was seen but not removed papilledema completely disappeared.

Leslie Paton and others have spoken of the frequency with which patients suffering from papilledema complain of transient amblyopia: seven of my patients complained of this symptom and spoke of it as having been productive of very considerable distress.

Bordley and Cushing[19] in a recent communication have advanced the suggestion that in cases of heightened intracranial pressure there is a marked diminution in color perception, and in cases in which there obtains gradually increasing pressure on an optic tract it has been long recognized that in the earlier stages of the disease there may be complete color-blindness in the opposite visual field, with retention of all other forms of visual perception.[20] An examination of the pathological findings in my patients suggests the probability of hemianopia or hemiachromatopsia having been present during life owing to the proximity of the growth to the optic tract and radiations. In all cases the existence of hemianopic defect was considered and negatived as the result of examination.

Five patients were examined perimetrically for various colors; the sole abnormality discovered was the concentric contraction of the visual field so often associated with severe, and especially with protracted, papilledema.

Fits

Under this generic title I shall describe the several varieties of pyschical and physical phenomena arising presumably as the result of irritation of cerebral centers by tumor growth in the temporosphenoidal lobes.

It seems most convenient as a preliminary measure to divide these into *major*—those attacks in which consciousness was lost— and *minor*—those in which consciousness was retained though in some cases transformed.

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19. Bordley and Cushing, H.: Arch. Ophth., 1909, xxxviii, 451.
20. Swanzy, Sir Henry: Oliver and Norris' Diseases of the Eye, N. iv, 552.

All but two patients of my series (Cases 3 and 6) suffered at some time or other from sudden attacks of loss of consciousness, associated with cyanosis, stertorous respirations and in four cases generalized convulsions were also present, with tongue-biting and sphincter relaxation.

These seizures, in themselves, present little to distinguish them from those commonly seen in patients suffering from epilepsy of so-called idiopathic origin, but it is to be noticed that in all, a warning or "aura" of some kind was present, and in all, some disability either in speech or in the motor and sensory systems followed the attack. Patient 2, who had her only major attack in the hospital was found to have a condition of reflexes after the fit had passed, signifying that a greater stress had fallen on the right hemisphere than on the left—the left abdominal and epigastric reflexes being abolished, while their fellows were but slightly diminished—and the left plantar reflex being of extensor type in contrast to a flexor response on the right side.

In two other cases (1 and 5) there was a history of postepileptic weakness in the limbs contralateral to the tumor, and patients 5, 6, 7, 8 gave an account of transient difficulty in speaking after each attack; the nature of this will be dealt with later.

Those attacks which were not associated with definite loss of consciousness were of so varied a nature as to demand examination in detail.

Dr. Hughlings Jackson[21] was the first to draw attention to a type of epilepsy in which the general attack was associated with subjective sensations of taste and smell. These, he considered, were due to irritation of the anterior poles of one or other temporosphenoidal lobe, where Dr. Ferrier by experiment had succeeded in localizing the centers for these senses. Following the clue given him by Ferrier's experiments, he called such seizures "uncinate fits," and later was able to prove the correctness of his hypothesis by the examination of the brains of persons who, during life, had been subject to epilepsy of this description.

Sander,[22] Lockemann,[23] Westphal[24] and Schlager[25] all reported cases of general epilepsy preceded by subjective sensations of smell, in which tumors were found involving the frontal and temporal lobes; in all of these early cases, however, the olfactory bulbs or tracts were affected together with the hippocampal gyri, and from them no precise conclusion could accordingly be reached regarding the functions of the last-named convolutions.

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21. Jackson, Hughlings: Med. Times and Gaz., 1876.

22. Sander, Wilh.: Epileptische Anfälle mit subjektiven Geruchsempfindungen etc., Arch. f. Psychiat., 1873-1874, iv, 234.

23. Lockemann: Ztschr. f. ration. Med., xii, 340.

24. Westphal: Allg. Ztschr. f. Psychiat., xx, 485.

25. Schlager, Ludw.: Ztschr. d. Gesellsch. d. Aerzte zu Wien, 1858.

In 1882, however, McLane Hamilton[26] of New York published a case of a woman who had sustained a head injury in childhood and afterward was subject to sudden attacks "of disagreeable odor, sometimes of smoke, sometimes of a fetid character, which rose in her head and choked her"—an experience almost invariably followed by general epilepsy. She died of phthisis two years after coming under observation, and was found to have a hemorrhagic pachymeningitis localized to the anterior and inferior part of the right temporosphenoidal lobe. The olfactory bulbs and nerves were unaffected.

In 1886 Anderson[27] reported a case of pituitary tumor involving the left temporosphenoidal lobe in which during life there had been paroxysmal attacks of "a rough, bitter sensation in the mouth" with chewing, spitting movements and other phenomena to which reference will be made later.

Dr. Jackson[28] also drew attention to peculiar, transient, psychic variations of somewhat elaborate character occurring as an expression of unstable nervous control, and often heralding or replacing a severe epileptic convulsion.

Complex intellectual states occurring as the initial stage of "grand mal" were alluded to by Herpin[29] in 1867, who reported the following case:

> Une jeune personne d'un ésprit très-observateur racontait ainsi le début de ses attaques: "Je suis prise, sans cause, d'une tristesse subite, et à l'instant même mes yeux restent fixés sur un objet et ma pensée sur une idée qui me rappelle l'image très-nette d'un ancien rêve; l'idée fixe m'absorbe tellement que, quoique je regarde toujours vers le même point, je ne vois plus d'objet."

This "voluminous mental state" as described by Dr. Jackson was often associated with those crude sensations of taste or smell which have been mentioned above as being due to irritation of the uncinate gyri, and masticatory movements have been frequently observed suggestive of a discharging lesion in the neighborhood of the gustatory centers. As a third association with dreamy states may be cited an epigastric sensation, invariably unpleasant and often accompanied by a feeling of intense fear.

It is not claimed that these incoordinated resuscitations of sensory impressions, now known as dreamy states, can occur only as the result of gross irritation of the temporosphenoidal lobes, but rather that in

26. Hamilton M'Lane: On Cortical Sensory Discharging Lesions, New York Med. Jour., 1882, xxxv, 582.

27. Anderson, James: Sensory Epilepsy, Brain, 1886, ix.

28. Jackson, Hughlings: On a Particular Variety of Epilepsy, etc., Brain, 1888-1889, ii, 179.

29. Herpin: Des accès incomplets d'épilepsie, 1867, quoted by H. Jackson.

those cases in which they occurred, and organic intracranial disease was later found to be present, the lesion has invariably been found to be situated in the temporal lobes.

That they may occur in persons who are to all outward appearance in perfect health is patent when one considers how many references to them are scattered through the entire body of English literature; nor need inquiry among apparently normal individuals be far extended before a "subject" be discovered.

Descriptions of dreamy states show extraordinary variations, possibly dependent on the severity of the attack, on the causative factor of the attack, and certainly to a great extent on the power of the patient accurately to observe his experiences, and later to clothe them in language sufficiently concrete to be intelligible.

The dreamy state is seldom associated with actual loss, but rather with an alteration of consciousness; the patient suddenly becomes aware of everything being changed, yet very familiar; a feeling of reminiscence, as though everything had happened before, so long ago that measurements of time are transcended; the feeling of old-time familiarity is so acute that it seems as though it *must* be that he *surely* knows what is about to happen; what the next word in the conversation will be; what the next movement of his companion will bring about. The sense of prescience is so acute as to give mental pain because of its inevitable unfulfilment; he stands for an instant on the very edge of the "unknowable"—the veil is about to be torn away—and then, as suddenly as it came, the elevation of consciousness is gone and the commonplace returns. That the condition is not of the nature of a memory is apparent on questioning the more intelligent of those who experience it; it is not even a memory half-grasped but still elusive—that, at least, is tangible though evasive; it is of ordinary experience and subject in the greater part to conscious control, but *this* is beyond all things, beyond thought or wish, and beyond language to portray.

It has been said[30] that attacks such as these are not found in the uneducated or in persons incapable of entertaining abstract ideas, but is it not more probable that subjects of lower mental development are unable lucidly to narrate psychical phenomena of such varied and nebulous character as tax to the utmost the descriptive powers of some of the greatest masters of the English tongue?

Tennyson says:

> As when with downcast eyes we muse and brood,
> And ebb into a former life, or seem
> To lapse far back in some confused dream,
> To states of mystical similitude;

30. Crichton-Browne, Sir, James: Cavendish Lecture, Dreamy Mental States, 1895, p. 7.

And again in "The Two Voices":

> Moreover, something is or seems,
> That touches me with mystic gleams,
> Like glimpses of forgotten dreams—
>
> Of something felt, like something here;
> Of something done, I know not where;
> Such as no language may declare.

Where defeat is almost acknowledged by such a singer, how can we expect mute and inglorious patients to succeed!

Of the present series, seven patients gave an account of attacks of "coming over dreamy," during which they looked "dazed and lost," but only two, both of whom were exceptionally intelligent, were able much further to elaborate their descriptions.

The type of dreamy state which I have attempted to describe is probably the least complex of those which are found associated with gross intracranial disease; in a considerable number the irritation of the higher mental centers produces, not merely "a peculiar thought" as a man under Dr. Coats'[31] observation expressed it, but a subjective projection of that thought, so that before the patient there appears, as it were, a mirage or, more commonly, specter faces.

It may be said, however, that certain elements—defective objective, and increased subjective consciousness, and a sense of reminiscence, run through all these primitive forms of mentality like the theme in an opera.

It is well-nigh impossible to classify the various modifications of dreamy states which were present in these cases: indeed, the terms in which several of the patients described their attacks were so vague that no paraphrase could successfully convey their meaning.

For over twenty years my first patient had had epileptic fits of ordinary character and without auræ, at intervals of three to six months. In May, 1907, while dressing, she suddenly heard a bell ringing, then saw a "strange bad woman" clad in rags, and smelt a most evil odor which originated, she thought, in the stranger's clothes; she felt terribly afraid "as though some awful thing were about to happen"; nausea was present and she complained of pain around the heart, and in the pit of the stomach, and tingling throughout the inner aspect of the left upper limb. For some seconds she seemed dazed and frightened, then screamed, became suddenly unconscious and passed through all the stages of a severe epileptic attack which in no way differed from her previous fits.

While in the hospital she had several such attacks in which, however, the sensation of dread was often the first warning of the onset of

31. Coats: Brit. Med. Jour., 1876, ii.

a fit, and in the stress of this emotion her facial expression invariably was that of one "facing an expected horror" [32] (compare Case 2).

The psychical projection in this case, in its elaboration and the constancy of its recurrence, resembled that of a patient of Dr. Hughlings Jackson and Dr. Beevor,[33] in which, however, the vision of the "little black woman engaged in cooking" was not associated with any sensation of terror, but on the contrary was rather agreeable than otherwise.

Neither of these patients was deceived as to the unsubstantial nature of her visitor, nor among other cases I have seen or read of was there one in which the patient doubted the subjective nature of the phenomenon. An important feature of V. F.'s attacks was the occurrence of tingling in the left arm and hand, due to "spread" of excitation to the post-Rolandic cortex—theoretically a probable and frequent event but in reality of rare occurrence as a result of tumor growth in the temporosphenoidal lobes. Anderson's patient,[27] to whose case reference has already been made, had attacks in which there was a combination of crude subjective sensations of taste with dreamy reminiscences of considerable complexity, prefaced by a "peculiar sensation" in the arm and hand contralateral to the tumor.

It is necessary now to consider the experiences of my second patient —a schoolmistress and an exceptionally intelligent woman. She was admitted in July, 1907, complaining that for two years she had been subject to "nervous attacks . . . sudden, inexplicable shocks associated with an indescribable feeling of terror and apprehension, which would pass off in a minute or two and leave me weak and trembling." There was no loss of consciousness. These sensations were apparently causeless, and occurred several times daily quite independently of what she might be doing at the moment.

Her general health was unaffected. From January, 1907, she could distinguish two types of seizure:

1. Major attacks occurred daily, beginning with "an overpowering sensation as if I am going into a sound slumber . . . a kind of dreaminess; . . . I feel prostrate . . . I know where I am, but my feelings seem unreal: a far-away unearthly feeling . . . I know that I am myself all the time, neither I myself nor the things around me are changed, but the relationship between myself and them is altered. I do not think I can speak in these attacks. I was in one when Sister came round a little while ago: I knew she was near, but I could not take the medicine; I could not explain to her why I could not take it. I do not think I can move in these attacks.

"Sometimes there is a kind of buzzing, whirring sound, which seems unreal though not far off. I do not take any interest in things, though I am aware of them. I always try to find out what the attack is like; I am sufficiently con-

32. Jackson, Hughlings and Stewart Purves: Case of Tumor in the Right Temporosphenoidal Lobe, Brain, 1899.

33. Jackson and Beevor: Brain, 1889-1890, xii, 358.

scious to try to remember what I am experiencing in order to tell the doctors about it. Nearly always there is a terrible sensation of fear; I am aware there is nothing to be afraid of; but the feeling of pure fear is as bad and horrible as it was at first" [a reference to the attacks originating eighteen months before].

"This fear is not associated with any object or person whatever—I *know* everything is all right but, nevertheless, this dread [of nothing] persists during practically the whole of the attack."

She had no visual phenomena, and she had neither defective orientation of her limbs nor feelings of transference of herself in time or space. Neither was there any sense of disturbance of the size of herself or parts of herself. (Anderson's patient had a sensation of "swelling" in the hand contralateral to the tumor.) "My children always know when I am going to have an attack because of the movement of my face; they tell me I make champing, sucking movements and twist my mouth about."

These attacks were not essentially associated with sensations of difficulty in breathing or with any cardiac sensations, which were more often present in what she called:

2. Minor attacks occurred ten or twelve times a day. They varied much. "It's a sudden feeling of hopeless despair, though I'm naturally always in good spirits. . . . I know there is nothing to be despondent about . . . It's not in relation to any of my thoughts or ideas. I do not despair *about* anything. but it's just as hard to bear for the time being" . . .

"Other unhappy, uncomfortable sensations may constitute the attack, which I can't find adjectives to express . . . I want to know what they are all about . . . they seem so strange, and without cause . . . These sensations never seem to be real . . . even when I am feeling them. I know they have no cause, but I can't throw them off."

In August, 1907, this patient for the first time began to have frequent subjective sensations of smell:

"It comes several times a day, and bears no relationship whatever to my other attacks. . . . I am quite certain of this. It often lasts as long as ten minutes; it seems to be in the ward round about (never in the nostrils); it seems to come from somewhere on my right; what makes me think it is my own creation is that I know I don't really smell anything."

"This smell is neither pleasant nor unpleasant; it is not of the nature of a scent nor a perfume but rather like something in a factory or a brewery; it is quite unfamiliar. . . . I have never smelt anything like it before."

She never had any subjective sensations of taste.

On Oct. 16, 1907, she was sitting up in bed writing a letter, when she suddenly felt "a strange sensation of dread . . . of being overpowered . . . overwhelmed."

"At the same time I felt my neighbors must have known what was wrong with me, that they must be looking at me. . . . I seemed almost to know what was passing in their minds about me . . . just as if there must have been some 'wireless telegraphy' between myself and them. Then things seemed different as though I were somewhere else . . . there were a lot of loud voices. . . . I don't remember any more" . . .

She then uttered a shrill cry and fell backwards and to the right: she became cyanosed and breathed stertorously. The left side of her face was contorted; the upper extremities were adducted and semiflexed at the elbows; the hands were tightly clenched. This rigidity was maintained for a few seconds and succeeded for some ten seconds more by slight jerking movements of all four limbs.

Five minutes after the return of the corneal reflexes, she was found to have marked weakness in the left side of the face, of supra nuclear type, exaggeration of the deep reflexes on the left side, abolition of the left abdominal and epigastric reflexes, while the plantar response of the same side was definitely of the extensor type. The reflexes of the right side were normal in all respects.

Reference may now be made to the five remaining patients of my series who complained of sensations analogous to those I have just described.

Patient 3 never complained of "attacks" at any time; he spoke of frequently hearing "a sound like singing," which, however, he was unable to describe in any further detail.

Patient 4, for three months previous to admission to the hospital, was subject to "sudden attacks of faintness and dreaminess" during which—according to his wife—"he looked dazed, and had a far-away look in his eyes."

These fits were frequently accompanied by a "sudden taste in the mouth—like ink," and a sensation of smell, which he never described but always complained of.

He was under observation for but three days, during which he was evidently suffering from very severe general intracranial pressure with consequent mental impairment; further details of his seizures were therefore not obtainable.

Patient 5 was subject to "sudden attacks of strangeness . . . I get a swimming in the head, not a dizziness exactly . . . I feel dreamy . . . but I don't lose myself," i. e., he did not lose consciousness. This patient never had subjective sensations of any special sense.

Patient 6 had had attacks since May, 1907, in which he "looked dazed and lost." He did not lose consciousness in these seizures, but while they were in progress he became completely unable to recognize his surroundings or to tell where he was—and although he had been a sailor for many years he was without power to distinguish the points of the compass as long as this curious mental state persisted. He never suffered from loss of consciousness nor convulsions, nor had he at any time any crude sensations of smell and taste.

Almost completely analogous to the condition of this patient is that of one reported by Sir James Crichton-Browne,[34] who "in youth and manhood was distressed by brief seizures which may be described as loss of orientation, but which he himself nicknamed "a topographical topsy-turvy." Generally, when out walking and alone, his consciousness of his geographical bearings became momentarily confused, and this without vertigo or apparent movement of objects from side to side.

Patient 7, for three months before coming under observation, had suffered from frequent subjective sensations of taste and smell, "like a vapor in the mouth . . . like the smell of smoke . . . the smoke of a foul pipe . . . coarse tobacco." This sensation prefaced three attacks of loss of consciousness and generalized convulsions, but also frequently occurred alone. The patient had no dreamy states.

Patient 8 was a woman who had had, as was found at the operation, long-standing ventricular distention; in addition to suffering from a considerable degree of aphasia, she was mentally inarticulate. For seven years she had been subject to attacks of major epilepsy, prefaced by "a horrid smell of rotten fish," and followed by transient difficulty in speech. In addition to these more serious manifestations she had frequent sudden attacks "of coming over dreamy," which may have been the result of increased intracranial pressure but which, in so far as each was invariably preceded by an olfactory aura, were in all probability produced by a discharging lesion in the region of the uncinate gyrus of one or other side, spreading to the adjacent temporosphenoidal convolutions.

This patient had many such seizures when under observation; she would suddenly exclaim, "Oh, the smell," make smacking and spitting movements with the lips, and gestures of disgust and repulsion. Her face would become pale and anxious, and her eyes fixed on some far-distant point. She usually answered if spoken to, but in a low colorless voice; consciousness was never lost and the reflexes remained unchanged. The duration of such seizures was usually about two minutes.

During the five months previous to admission to the hospital, Patient 9 complained of "an almost constant horrible taste in the mouth." For the same period she was subject to momentary losses of consciousness, with frequent sudden lapses of memory for the names of familiar objects; she had no dreamy states.

Speech Defects

From cases of neoplasms producing functional depression or destruction not only of sharply limited and contiguous zones of brain tissue, but also of areas situated at distances varying directly with the size of the tumor, the rate of its growth, and the degree of ventricular distention

34. Crichton-Browne, Sir James: Dreamy Mental States, p. 16.

it has created, it is impossible to procure precise data of the cerebral localization of the several attributes of speech.

Such data have been acquired by the study of the effects of experimental lesions, and by the investigation of cases in which the lesions were of sudden origin, of definite limitation, and decisively destructive in their results.

The effects of tumor formation in or near centers concerned in speech, thus localized, differ materially from those produced by vascular lesions in the same situation, and consist, at least in the earlier stages of the disease, in deterioration rather than in abolition of function of the centers and their annexes.

We are now more immediately concerned with the auditory center, which, as has been shown above, is probably situated in the transverse temporal gyri of Heschl and the posterior three-fifths of the superior temporosphenoidal convolution. The subdivision of this center into one area immediately concerned with the appreciation of ordinary and of musical sounds, and another, reserved for the interpretation of heard speech, may for our present purpose be neglected, inasmuch as the size of the lesion in these cases precludes the possibility of such minute differentiation.

The center for heard speech is almost certainly situated in the left hemisphere in right-handed persons; in nearly all cases of sensory aphasia occurring as the result of injury to the right temporosphenoidal lobe, some anomalous circumstance has been discovered to account for the condition. It was found by Oppenheim[35] in two cases of affection of the right temporal convolutions that in one, there was acquired left-handedness in a woman aged 59, who had been forced to use her left hand for all purposes owing to injury at the age of 17 years; in the other case, there were two tubercles in the right temporosphenoidal lobe and aphasia is reported to have appeared only when the patient was already moribund, and—according to Oppenheim's assumption—as the result of toxic action on the auditory speech center in the left side of the brain.

On the other hand, sensory aphasia was absent in a case of tumor of the left temporosphenoidal lobe reported by Westphal,[36] but here the patient was left-handed.

These anomalous cases in no way disprove the overwhelming evidence which establishes, as securely as anything can be in medicine, that in right-handed persons destruction of the posterior part of the left superior temporal gyrus will produce inability to understand heard speech, and abolition of all memories for spoken words; that destruction of the left supramarginal and annectant gyri will cause failure to understand writ-

35. Oppenheim: Quoted by Bruns in Geschwülste des Nervensystems.
36. Westphal: Bruns in Geschwülste des Nervensystems.

ten speech or even will abolish the power of recognizing familiar objects; and that failure to recollect the name of an object seen and recognized will follow the destruction of the association tracts between these two centers.

Variations in bulk, position, and rapidity of growth, in tumors of the temporal lobes produce changes in the degree, and to a lesser extent in the type, of speech defect found in different cases; but there is one characteristic which may be said to be constant: a depression of the power to recall words, especially the names of persons, places and objects. This word-forgetfulness may be manifest in two different ways, either as inability to recollect a name in the course of ordinary conversation, or a failure to name an object of which there is visual recognition. At first sight there may appear to be no essential difference between these two defects, but it must be pointed out that the former depends on a depression of function in the cortical area containing the memories of words, while the latter arises from an interruption of the subcortical tracts uniting the visual and auditory centers.

Patients suffering from a functional deterioration of the auditory word centers do not experience true loss of word memory; the memories are for the most part still intact, but their facilitation for the moment becomes more difficult and the patient is unable by force of will to bring them above the threshold of consciousness, below which they lie latent and beyond his conscious grasp.

Abundant proof of this statement will be forthcoming when we consider the speech defects of these patients, but to illustrate my meaning a conversation with H. G. (Case 7) may here be quoted:

"I went to see Dr. Jacob . . . No! not Jacob . . . What's his name?" Here he looked at the card above his bed on which was printed the name of his physician. "Taylor! that's it."

"How did you go to his house?"

"I went by the underground terminus . . . No! what *do* you call the thing?"

"Twopenny Tube?"

"No! that's not the name."

"London Central Railway?"

"Yes! that's it."

"Where did you get out?"

"Oxford Terminus. . . . No! . . ."

"Oxford Circus?"

"Yes! that's the name."

"Where did you go then?"

"You take two stations."

"Stations?"

"No! turnings . . . that's it . . . to Wegley Street . . . No! . . . Welbeck Street."

From this it is evident there was neither word-blindness, nor word-deafness; further, word-memories were not impaired, but merely sub-

merged, and capable of being brought up to consciousness by a great volitional effort, or, more usually, by the aid of an additional cognate auditory or visual stimulus.

As has been shown the difficulty in speech in these cases consists almost entirely of a failure to recall proper names and nouns, for which defect Kussmaul[37] offers the following explanation:

> The more concrete the idea, the more readily is the word to designate it forgotten when the memory fails. Probably the only reason for this is that the conceptions of persons and things are more loosely connected with their names than are the abstractions of their circumstances, relations, and properties. We easily represent persons and things to ourselves without names; the image of sense is here more important than the symbol—i. e., the name, which conduces but little to our comprehension of personages or objects.
>
> More abstract conceptions, on the contrary, are attained only with the aid of words, which alone give them their exact shape. Hence verbs, adjectives, pronouns, and still more, adverbs, prepositions and conjunctions, possess a much more intimate relation to thought than nouns. We can conceive that the processes of excitation, and the combinations in the cellular network of the cerebral cortex must be much more numerous for the creation of an abstract than of a concrete conception, and that the organic tracts which connect the former with its name must be correspondingly much more numerous than those of the concrete.

This inability to recollect names results in a mode of expression which which may be termed elliptical or figurative. The various attributes and associations of the object, the name of which cannot be recalled, are well remembered and properly described. Patient 7, when asked what he had for breakfast said:

> "Oh! some . . . I can't think of the word for it . . . I know what it is . . . You have sugar with it. I know that."
>
> "Porridge?"
>
> "Yes! that's the word . . . Then some chocolate. No! not chocolate . . . I can't think of the name . . ."
>
> "Coffee?"
>
> "That's it . . . Then bread and butter."

Another (Case 8), when shown a sovereign described it as:

> "Good to have . . . gold coin . . . money."
>
> "Is it a sovereign?"
>
> "Yes! that's what it is."

A letter she described as "a bit of paper," yet an envelope was called "something to put a letter in."

Patients 5 and 9 substituted similar descriptive phrases for the names of familiar objects, a note-book being called "something to write in" and a fountain-pen "one of those patent pens."

Patients whose faculty of word recollection is still further degraded have remarkable difficulty in preventing the inapposite recurrence of a word, the facilitation of which has already been accomplished; their mistakes are perceived by them as soon as they are uttered—considerable

37. Kussmaul: Ziemssen's Cyclopedia, xiv, 759.

distress is produced—but a minute later the identical error again is made.

A bunch of keys was shown in Case 6:

"I know those . . . made of wood . . . No! of iron."
"What are they for?"
"To lock the door with . . . I can't think of the word."

Shown a pocket knife—"a shovel put in a pocket"; when given the opened knife he shut it and said "knife" at once.

Shown a pencil "shovel," but when it was given to him he used it correctly.

Shown a watch he named it properly, but on being then shown a match he said "watch chain," yet when it was given to him he made the movements of striking a light.

When shown a handkerchief he said "watch . . . no! handkerchief"; but a penny being then produced he said "handkerchief . . . handkerchief . . . handkerchief . . . No! penny!"

Verbal perseveration in spontaneous speech is the result of decreased excitability of the auditory word center and occurs physiologically in fatigue[38] and old age. But the preponderating factor in the causation of perseveration of inapt expressions, in spite of visual stimuli, received and comprehended, must be a loss of function in the occipitotemporal association fibers.

So far were these patients from being word-deaf that often the auditory path was the only avenue by which recollection of words could be stimulated, and it must be emphasized here that not one of the five patients—5, 6, 7, 8, 9—in whom the growth occurred in the left hemisphere producing difficulty in the recollection of words, had the slightest degree of word-deafness. Spoken commands were accurately performed; their verbal mistakes were immediately recognized as such on being uttered and heard; and their power of discrimination of the value of words was exhibited by the fact that an inaccurate prompting was invariably rejected.

Reading aloud and copying were both well and intelligently carried out; writing to dictation was less well performed. As an example of spontaneous writing in which as in other cases, word forgetfulness and perseveration are manifest, may be appended a letter written by Patient 7 to a friend who was ill:

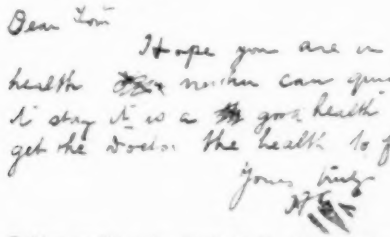

Fig. 1.—Letter written by Patient 7, showing loss of word-recollection and perseveration of error.

38. Myers: Text-Book of Experimental Psychology, 1909, p. 144.

Before leaving the subject of the type of aphasia found in these patients it may be stated that in no case was there any defect in articulation, and that the four patients in whom the growth was in the right hemisphere, failed to show any disability in speech whatsoever. In all these cases the patients were right-handed.

Special Senses

Taste and Smell: Notwithstanding the evidence of irritation of the olfactory and gustatory centers, which was obtained in so many of these patients, in no case was there absolute loss of the sense of smell or taste; in only one (Case 2) was there relative loss, and it was uniformly bilateral.

Hearing: Cases have been described from time to time of complete unilateral deafness, resulting from destruction of the opposite auditory center, but this effect has not been experimentally obtained. Moreover, Gowers[39] is opposed to the possibility of such a condition being other than transient, and the same contention is maintained by Bruns,[40] who states that acute lesions of one or other auditory centers are accompanied by a merely temporary deafness in the opposite ear. Further, on anatomic grounds, owing to the incomplete decussation of the cochlear fibers of the auditory nerves,[41] each auditory center is probably connected with both labyrinths. Munk affirms the contrary, but Lewandowsky[42] has experimentally proved that dogs retain perfect hearing after the removal of the labyrinth and auditory center of the same side.

Beevor[2] quotes three cases, one of complete, and two of partial deafness in the ear away from the tumor, but he does not state the condition of the peripheral auditory apparatus.

Two of my nine patients heard imperfectly on the side contralateral to the tumor; another (Case 6), whose tumor was on the left side, was unable either by air or bone conduction to hear in the right ear; this condition was of old standing, and was attributed by the patient—a gunner—to a big-gun practice, after which he had suffered from considerable right-sided earache without deafness; it was not until a few months later that he noticed that his hearing was defective.

In these three cases the tympanic membranes were normal.

In my other cases hearing was unaffected and we must conclude that in temporal tumors, auditory compensation by the opposite center usually occurs *pari passu* with the tumor growth.

Visual acuity was affected to the extent stated in each case (see appendix) merely by the changes associated with papilledema. The

39. Gowers, Sir William: Diseases of the Nervous System, ii, 284.
40. Geschwülste des Nervensystems.
41. Schafer and Symington: Quain's Anatomy, iii, part 1, p. 139.
42. Lewandowsky: Die funktionen des zentralen Nervensystems, Berlin, 1907.

improvement in vision which ensued after operation, while not differing from that hitherto recorded, is worthy of special consideration, as it emphasizes the advisability of operative interference at the earliest possible date in all cases of cerebral tumor in which papilledema is present.

CASE 1.—Admission, right, 6/24; left, 6/12. Discharge, right, 6/9, left 6/6.

CASE 2.—Admission, right, 6/60; left, 6/30. Discharge, right, 6/12; left, 6/12; 6/9 with binocular vision.

CASE 8.—Admission, right, 6/24; left, 6/12. Discharge, right, 6/9; left, 6/6.

In Cases 5, 6 and 7 visual acuity materially improved after operation, but no detailed examination was made before discharge.

Cranial Nerves

The first and second cranial nerves have already been considered.

The proximity of the third nerves to the temporal lobes would seem to render them especially liable to damage by pressure from tumors in these areas, and Knapp[43] lays considerable stress on homolateral or, less frequently, crossed partial third nerve paralysis, as a diagnostic sign of tumors of the temporosphenoidal lobes. In none of these cases was this result observed, nor was it present in the other cases of temporal tumor which have come under my observation.

When a temporal lobe is the seat of abscess it is, however, not very uncommon to find ipsolateral ptosis, mydriasis and external strabismus —a statement which agrees with Bruns' experience, and has been emphasized by Risien Russell in the Lettsomian lecture for the present year.

Three patients had a history of transient diplopia, probably due to temporary increase of pressure on the third or sixth nerves; in two, the ipsolateral pupil was myotic, though active to light and on convergence, while in the same patients there was nystagmoid jerking of the eyeballs on conjugate deviation to one or other side—probably a pressure-effect on the cerebellum.

The fifth nerve was in all cases unaffected.

Seventh Nerve

Peripheral affection of this nerve was in all cases absent, but in no less than five out of the nine patients there was marked supranuclear weakness of the face contralateral to the tumor out of all proportion to the degree of paresis of the limbs of the same side.

This striking fact is, however, only corroborative of Horsley's statement[44] in 1895, that in those temporal tumors the pressure of which is directed upward there is definite sequence in the progress of the paralysis, it being more marked first in the face, then in the upper, and last of all

43. Knapp: Quoted by Bruns in Geschwülste des Nervensystems.
44. Horsley, Sir Victor: Clin. Jour., Lond., v, 249.

in the lower extremity. In four of these five cases, however, in which the face was markedly affected, another point was noticed, that, contrary to what is usually seen in facial paresis of supranuclear type, the emotional expression was either lost or greatly diminished on the affected side.

There can be no doubt that this condition was the result of pressure acting on the optic thalamus, which Nothnagel[45] and Bechterew[45] showed many years ago to be an important reflex center for emotional expression.

The phenomenon was best shown in reflex action, as when the patients were made to laugh by being tickled; when this was done to the eighth patient, in whom the condition was most noticeable, the left side of the face wrinkled in laughter, while the right side remained motionless and smooth for some five seconds, after which the right angle of the mouth was elevated, but to a much less degree than that of the opposite side.

Acuity of hearing has already been referred to.

The remaining cranial nerves were unaffected.

Motor Symptoms Apart From Those Due to Affections of the Cranial Nerves; Deep and Superficial Reflexes

Patient 1 said she felt that her left arm and leg were weaker than their fellows, but examination failed to show any difference in strength between the two sides. Her gait was normal. The deep reflexes were everywhere brisk and respectively equal on the right and left side. Both the plantar responses were of the flexor type, but the left abdominal reflexes were markedly depressed, and on repeated stimulation tired much more quickly than the right.

Rosenbach was the first to point out in cases of hemiplegia the absence of the abdominal and epigastric reflexes on the side of the affected limbs, and now they must be regarded as the most sensitive indication of commencing pressure on the pyramidal tracts.

Grainger Stewart[46] has pointed out their significance in cases of frontal tumor, in which there is backward pressure on the precentral cortex, and their importance in this series is apparent, as in five cases their inequality was a material aid to diagnosis.

The second patient was without motor symptoms, when she came first under observation, but in the course of the following six weeks her left leg gradually became weak, though it was not possible to detect any loss of strength in the left upper extremity.

This evidence of slowly cumulative pressure on the peripherally placed leg fibers of the internal capsule corroborated that given by the condition of the reflexes of the left side, the superficial being depressed

45. Soury, Jules: Le systeme nerveux central, 1343-1344.
46. Stewart, T. G.: Lancet, London, 1906, p. 1209.

and the deep exaggerated, though the left plantar response remained of the flexor type, except for a short time after the patient's only major epileptic attack.

In the third case, the depression of the left abdominal and epigastric reflexes was the sole indication of pressure on the pyramidal fibers: there was no loss of power in any limb, and the gait was normal. Neither patellar nor Achilles tendon reflexes were ever obtained, and this fact, together with the presence of double pes cavus, gave rise to the suspicion that Friedreich's disease might be a complicating factor: there was no further clinical evidence to support this hypothesis, and no degeneration was later found in the posterior or lateral columns of the spinal cord.

Degeneration in the posterior column of the spinal cord has been shown to occur with considerable frequency in cases of intracranial tumor, as a result of traction on the posterior roots by arachnoid distention, produced by increased intracranial pressure.[47]

The presence or absence of the deep reflexes has been usually directly dependent on the degree of this posterior spinal change, but absence of the knee-jerks in cases of intracranial tumor has been observed, when no demonstrable change had occurred in the cord,[48] particularly in those cases in which the growth was situated in the temporosphenoidal lobes.

Patient 4 had no loss of power in the limbs, nor were his movements ataxic while he remained in bed; however, his attempt to stand upright was very badly performed; he swayed directly backward, and in trying to maintain his balance took several quick steps backward on his heels, and would certainly have fallen had he not been supported. He said he had no dizziness but that he "just could not stand up straight."

Titubation of this kind has been described before as occurring in cases of temporosphenoidal tumor, and Sir Victor Horsley[49] is inclined to regard it as due to interference with Türck's bundle, which unites the pons and the posterior part of the temporosphenoidal lobe, where Mills assumes the existence of a center for orientation.

An identical phenomenon was observed in three more of my series (Nos. 5, 6 and 9), where it appeared, however, somewhat late in the course of the disease, when intracranial tension had become extreme, and cerebellar compression against the edge of the foramen magnum could no longer be excluded.

The condition of the reflexes in my fourth case was interesting: the left knee-jerk and both ankle jerks were absent; the right knee-jerk was much depressed; the abdominal and epigastric reflexes were not obtained on either side, while the deep reflexes in the upper extremities were equally brisk. The suspicion of tabes dorsalis being coexistent with cere-

47. Batten and Collier: Brain, 1899, xxii, 471 *et seq.*
48. Mackenzie, Sir Stephen: Brain, 1884, vi, 22.
49. Horsley, Sir Victor: Tr. Otol. Soc., London, 1905, vi, 77.

bral tumor was negatived during life by a cytological examination of the cerebrospinal fluid, and no degeneration was later found in any part of the spinal cord.

On admission to the hospital, my fifth case was entirely without motor symptoms, but the advent of right-sided weakness was heralded by a marked depression of the abdominal reflexes on the same side; it is to be noticed that by these alone the diagnosis as to the side of the tumor in the intracranial cavity could have been made two months before any weakness was found in the arm or leg of the same side.

Case 5 had no definite weakness in any of the limbs; the abdominal reflexes could not be obtained, probably because of the obesity of the patient; the plantar responses were both of the flexor type, but there was undoubted exaggeration of the deep reflexes of the right arm and leg.

In Case 7 the right arm was definitely weaker than its fellow, and the abdominal reflexes on the same side could only rarely be obtained, though those on the right were invariably brisk. There was change neither in quality nor degree in the plantar and deep reflexes.

In neither of the two remaining cases was there any affection of the limbs, nor were the reflexes altered in character.

The abdominal reflexes were not obtained in Case 8 until after operation and the relief of pressure: they were then found to be brisk and equal on the two sides.

The sole patient of this series who at any time had objective sensory change was V. F. (No. 1), who after the removal of the growth had slightly diminished acuity in appreciation of touch and pain on the left side of the body.

Appreciation of cutaneous pain and touch on the left hand was very slightly less than on the rest of the left side, but on the left hand touch sensation was very badly localized, pressure-pain was almost absent, and there was complete loss of the sense of position and of passive movement in the left wrist-joint and the finger-joints of the left hand.

As a result of this condition she was completely astereognostic in this hand, from which she frequently let objects fall, if she failed to keep her eyes fixed on what she carried. In March, 1910, she was in excellent general health and the sensory condition of her left hand was her sole complaint.

T. G. Stewart[46] has stated that loss of sphincter control is a frequent occurrence in cases of temporosphenoidal tumor, but such a condition was never present in any of these patients as long as consciousness was retained.

I do not purpose to detail the various considerations which led to correct diagnoses in all these cases; on all-important points emphasis

has already been laid, but to summarize them here may be convenient. Headache of varying severity and epileptiform convulsions are usually features of the beginning of the disease; fits may be very slight at first, consisting merely of loss of consciousness, a momentary tonicity and cyanosis, but a careful cross-examination will often elicit evidence of greater affection of one or other hemisphere. The presence of major attacks of this description may overshadow in the mind of the patient the occurrence of less pronounced seizures, in which consciousness is retained under altered conditions; a rightly directed examination will speedily discover such, if present, but we cannot expect all patients spontaneously to describe apparently negligible phenomena, if we ourselves fail to be alive to their vital importance. A history of crude subjective sensations of taste and small, occurring either alone or as the precursor of epileptiform convulsions, is of course of the first importance in the localization of disease in one or the other temporosphenoidal lobe, nor does it appear that we need expect any corresponding loss in acuity in the gustatory or olfactory senses.

Papilledema is usually present, usually intense, and usually more severe on the side of the tumor.

The presence of crossed facial palsy, particularly if it be of affective character, is especially valuable if the other signs of hemiplegia be doubtful. Particular stress must be laid on the condition of the abdominal and epigastric reflexes: these, with papilledema of greater ipsolateral severity and subjective auditory sensations of somewhat equivocal nature, were the sole positive signs in my third case; one of negative character was the complete absence of any defect in speech.

Word-forgetfulness has invariably been present in all my left-sided cases, though often to a very slight degree; even where it is not evident, it can be demonstrated if the examination be properly carried out, and tests should be mainly directed to the discovery of the ability of the patient to name known objects.

Word-forgetfulness was the only sign of localizing value in Case 9, and on it alone a correctly planned operation was performed.

The difficulty in the diagnosis of temporosphenoidal tumors, and in the localization of them in the right or left side of the brain arises not from the absence of indicating signs, but rather because signs, though present, are often not striking, are not looked for, and consequently are not seen.

Symptom-Complex of Tumor in the Right Temporosphenoidal Lobe, in a Right-Handed Person

Epileptiform convulsions, of varying severity and frequency; dreamy states or analogous pathological psychical conditions; crude subjective sensations of smell or taste with or without involuntary reflex move-

ments of mastication. Subsequent to major attacks: in most cases, transient weakness of the left lower facial muscles, usually most evident on emotional expression, less often the left arm and leg temporarily paresed; left abdominal reflexes diminished or absent, deep, increased; the left plantar reflex may be of extensor, and the right of flexor type.[50]

Bilateral papilledema, usually of greater intensity on the right side. Reflex change and motor symptoms on the left side, at first merely postepileptic, but later become persistent phenomena.

No word-forgetfulness after major attacks nor at other times. No speech defect whatsoever.

Symptom-Complex of Tumor in the Left Temporosphenoidal Lobe, in a Right-Handed Person

Difficulty in naming objects seen and recognized; later, word-forgetfulness in conversation; later, inapposite words and phrases, with instant recognition of mistake when made, but inability to prevent perseveration of verbal errors.

Reading aloud and writing to dictation are well performed. Spontaneous writing, poor.

Epileptiform convulsions of varying severity and frequency; dreamy states or analogous pathological psychical conditions; crude subjective sensations of smell or taste, with or without involuntary reflex movements or mastication. Subsequent to major attacks: in most cases, transient weakness of the right lower facial muscles, usually most evident on emotional expression—less often, the right arm and leg temporarily paresed; right abdominal reflexes diminished or absent—deep, increased; the right plantar reflex may be of extensor and the left of flexor type.

Bilateral papilledema usually of greater intensity on the left side. Reflex change and motor symptoms on the right side at first are merely postepileptic, but later become persistent phenomena.

APPENDIX: ABSTRACT OF CASES

CASE 1.—*History.*—V. F., female, aged 39, was admitted on June 15, 1908. From the age of 14 she had had, at intervals of three to six months, epileptic fits of ordinary character, but without auræ. In May, 1907, she, while dressing, suddenly heard a bell ringing, then saw a "strange bad woman" clad in rags, and smelt a most evil odor, which originated, she thought, in the stranger's clothes; patient then complained of a feeling of dread, associated with nausea, pain in the precordia and epigastrium, and tingling throughout the inner aspect of the left upper limb. For some seconds she seemed dazed and frightened, then screamed, suddenly became unconscious, and passed through all the stages of a severe epileptic attack, which in no way differed from her previous fits. A short

50. The presence of hemianopia or hemichromatopsia would of course indicate the side of the lesion, *vide* case reported by author at the New York Neurological Society, March, 1911.

period of drowsiness immediately followed and then, while yet dazed, the patient was very voluble, but subsequently she had no recollection of having spoken. Between May, 1907, and June, 1908, she had two or three less severe epileptic fits, each of which was preceded by nausea, vomiting and intense headache, mainly over the right occiput. In each of these attacks the auditory, visual, olfactory, and paresthetic auræ just described were accurately reproduced. At no time was there any word-forgetfulness or speech defect.

Examination.—Vision: Right 6/24, left 6/12; fields concentrically diminished, especially right; intense papilledema with hemorrhages on both sides; right: + 8D, left + 6D (3D hypermetropia in each eye); left pupil slightly larger than right; fine nystagmoid jerking on lateral movement, especially to left; no diplopia, ptosis, nor strabismus; ocular movements good; weakness of left lower facial muscles, especially evident in emotional expression; all other cranial nerves normal. Motor: Subjective weakness of left upper extremity only; no sensory changes; abdominal and epigastric reflexes were depressed, but more markedly so on left side; the deep reflexes were not appreciably affected.

Operation.—A well-defined deeply situated sub-cortical tumor, about the size of a tangerine orange, was removed from the anterior part of the right temporosphenoidal lobe.

Postoperative History.—Four hours after operation, the patient suddenly said she was going to have a fit; she experienced the same aura as before, after which her left forearm flexed, little finger and thumb extended, other fingers flexed, and a series of slow alternating flexion and extension movements of the wrist began and continued for ten minutes; consciousness was retained throughout. On August 11, patient was discharged in good general health. Mental state was normal; there was no speech defect. The swelling of the disks was rapidly subsiding. There was slight weakness of the left lower face and left arm, complete astereognosis in the left hand, with some diminution of tactile sensibility of the left side of the body. In March, 1910, the only pathological sign to be found was a loss of sense of position and of passive movement in the left wrist and finger joints.

Tumor.—Weight, 110 gm.; gliomatous, but sharply demarcated from surrounding brain tissue; tumor cells formed palisade arrangement around vessels, many of which contained organized clot; marked fibrous degeneration and thickening of vessel walls.

CASE 2.—*History.*—E. M., female, aged 32, admitted July 24, 1907, from 1905 had been subject to a sudden inexplicable feeling of profound fear, which lasted for one to three minutes, and left her weak and trembling. From January, 1907, she could distinguish two types of seizure.

1. Major: Usually once every day the patient felt overpowered by drowsiness, "as if on the verge of sleep" and "everything seemed remote, unnatural and unreal"; she could always recollect her experiences of these attacks, which were associated usually with a consciously subjective and groundless sensation of terror, and unnatural buzzing, whirring sounds in her head. Her children noticed that she always "twisted her mouth about and made sucking, champing movements" just previous to an attack.

2. Minor: These were slight attacks of inconstant character, but always consisting of unaccountable sensations, essentially unhappy, despairing, or uncomfortable. From Easter, 1907, the patient had frequent frontal headache and nausea, but rarely vomited; from the same period her vision rapidly deteriorated, till she was unable to read or sew. She never had diplopia, nor any speech defect.

Examination.—Intelligence and memory good. Smell and taste much impaired on both sides. Vision: Right 6/60; left 6/30; visual fields irregularly contracted; no hemianopia; swelling of right optic disc +3D, of left +5.5D; early atrophic changes in both: Paresis of supranuclear type of left facial muscles. No defect in other cranial nerves. Motor system normal. No objec-

tive sensory changes; frequently numbness and tingling in left face, preceded attacks. No sphincter trouble. Left abdominal reflexes diminished and readily fatigued; tendency to left ankle-clonus; left plantar response less definitely flexor than right.

Course of Disease.—August, 1907: Subjective sensations of smell first appeared: each subjective odor persisted for about ten minutes, recurred several times daily, was neither pleasant nor unpleasant, and seemed always unreal and to arise external to, and to the right of, the patient.

September 7: Vision: right 3/18, left 3/12; greater paresis of left lower face. Deep reflexes on left brisker than on right. Left abdominal reflexes greatly diminished. No other changes in former state.

October 16: Unconsciousness and general convulsions, with a doubtful origin in the left face. Five minutes after recovery: left facial weakness very marked; left abdominal reflexes absent, right present. Left plantar response, extensor; right, flexor.

October 29: Right temporal lobe exposed, and was found to be the seat of a hard, diffuse irremovable growth.

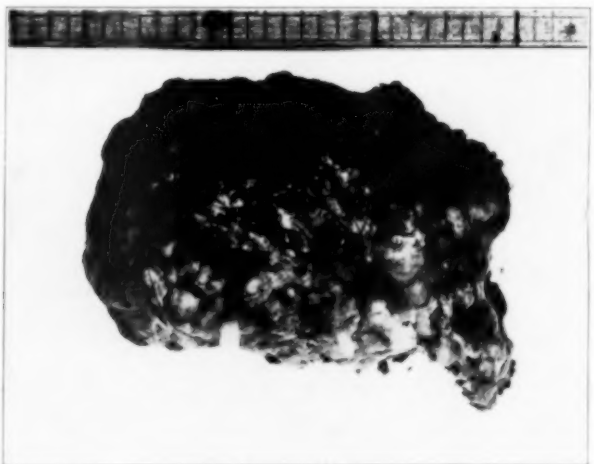

Fig. 2.—Tumor removed from Patient 3. Endothelioma weighing 92 gm.

February, 1908: General health excellent. No headache nor vomiting. Attacks decreased in frequency and severity. Marked subsidence of swelling of optic disks. No subjective sensations of smell; no speech defect.

CASE 3.—*History.*—T. B., male, aged 21, admitted Aug. 13, 1909. He, his maternal grandfather, mother, and brother, had all double pes cavus. From August, 1908, he had had three monthly attacks of severe frontal headache, nausea and vomiting, which lasted nearly twenty-four hours every three months. About June, 1909, slight dimness of vision developed, and four weeks later he was almost blind in the left eye. In July, 1909, a persistent "singing or burring" of increasing severity arose in the right ear; and just before admission the headache and vomiting recurred.

Examination.—Smell, Taste and Hearing: Normal. Vision: Right, 6/12; left, only light perceived. Fundi: Intense papilledema, 6D of swelling in each disk, with macular striation. No other cranial nerves affected. No motor nor sensory defect. No tremor or ataxia; knee- and ankle-jerks absent, with depres-

sion of deep reflexes in upper extremities. Plantar responses of flexor type. Abdominal reflexes on left, rarely elicited and easily fatigued; on right, brisk. Intelligence, attention and memory good. No speech defect or word-forgetfulness.

Operation.—On August 20 a large tumor, which involved the petrous portion of the temporal bone and which lay wholly below the Sylvian fissure, was removed from the right temporosphenoidal lobe.

Consciousness returned immediately after the operation and was retained till ten minutes before death, which occurred six hours later. During his conscious life after operation, there was no evidence of mental depression, difficulty in speaking, word-forgetfulness, nor motor nor sensory paralysis.

Necropsy.—Encapsulated tumor, weighing 92 gm., composed of endotheliomatous cells, without typical whorl arrangement. Anterior surface of petrous bone involved for a short distance; tympanic cavity not invaded. Brain convolutions much flattened. Into formation of tumor bed, all three temporal convolutions entered; upper limit, 1 cm. from fissure of Sylvius, lower, hippocampal convolution; brain compressed but not infiltrated.

CASE 4.—*History.*—B. C., male, aged 39, admitted Sept. 9, 1908. From June, 1908, he was subject to frequent sudden "attacks of giddiness," in which he felt "dazed" but did not lose consciousness. With each attack he experienced "a horrid smell, and a nasty taste like ink" and occasionally had in addition involuntary "twitchings" in the right arm. After July, 1908, he had three attacks of loss of consciousness and cya..osis, without involuntary movements or relaxation of sphincter control. Occasional vomiting and frequent nausea during July and August; frontal headache became severe in September; transient diplopia during the week before admission.

Examination.—Attention poor; patient talkative and excited; no speech defect; named seen objects perfectly. Cranial nerves normal except for intense swelling of both optic disks. Large recent retinal hemorrhage in the left eye.

Marked tremor in hands. Gait: On standing he carried himself solely on his heels and would have fallen straight backward had he not been supported.

Sensory system apparently normal.

Reflexes of the upper extremity brisk and equal on the two sides.

Right knee-jerk present, left knee-jerks not obtained. Ankle-jerks not obtained.

Plantar reflexes indefinite in character. No sphincter trouble. Cerebrospinal fluid normal.

Course of Disease.—September 10: Patient suddenly looked dazed and frightened, lay back in bed, marked flexion and extension movements at right elbow-joint. No march or spread of movement. Patient was asked if he could not keep his arm at rest and answered distinctly "No, I can't." Attack lasted about three minutes.

September 11: Patient suddenly became unconscious and greatly cyanosed. Breathing stertorous. Plantar reflexes both of extensor type

He gradually sank and died four hours later.

Necropsy.—Right temporosphenoidal lobe was softer and larger than left.

Section 1 along Sylvian fissure: Both lateral ventricles much distended and filled with blood-stained fluid. Cortex of anterior part of right superior temporal convolution was abnormally hard with loss of differentiation between gray and white matter. Chorioid plexus in lateral ventricles contained a few small cysts.

Section 2, 2 cm. lower: Tumor mass exposed, circular in outline, about the size of a tangerine orange. It lay about 2 cm. from the tip of the right temporosphenoidal lobe and reached to within about same distance from external aspect of lobe. It was external and anterior to the internal capsule and was the seat of a large recent hemorrhage. Much softening round tumor. Posteriorly, soft-

ening was extreme and the wall of the right lateral ventricle had given way; the posterior and descending horns were occupied by a gelatinous and blood-stained mass of debris. (Fig. 3.)

Section 3 through the tip of right temporosphenoidal lobe: The most extensive site of the tumor, which occupied most of the antero-internal part of temporosphenoidal lobe. Posteriorly the growth had involved the wall of descending horn of lateral ventricle. The uncus and pes hippocampi were intact.

Pons upper quarter of the Sylvian aqueduct dilated, old and recent hemorrhages.

Some clot in Sylvian aqueduct. No hemorrhages below the superficial origin of the fifth nerve.

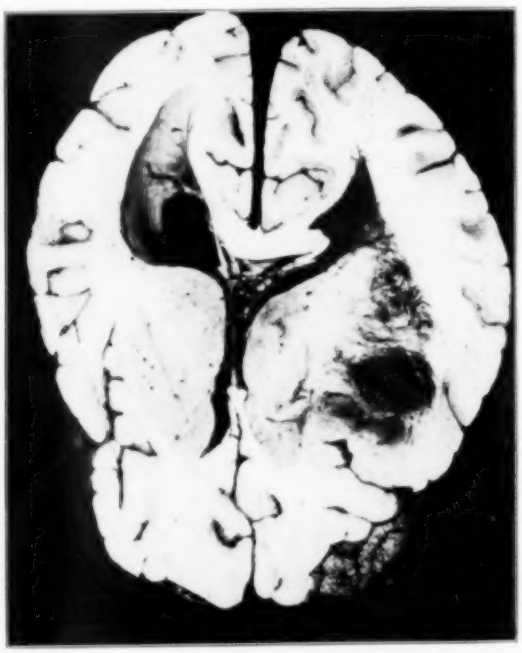

Fig. 3.—Brain from Patient 4. Section showing right temporosphenoidal tremor.

The spinal cord was normal.

On microscopic examination the growth was seen to be gliomatous.

CASE 5.—*History.*—F. J. B., male, aged 30, admitted July 7, 1908, on May 10, 1905, he suddenly felt dizzy and then for fifteen minutes was unconscious without convulsions or relaxation of sphincters. Subsequently he was subject to attacks which consisted of a "dazed and queer feeling" without loss of consciousness. From June, 1908, severe headache occurred, rarely accompanied by nausea and vomiting, usually in the early morning. From January to June he had difficulty in making himself understood; "he often used the wrong words"; and his memory gradually failed. Transient diplopia first appeared in June, 1908, and often recurred.

Examination.—Attention markedly variable; patient frequently unable to reply because he "cannot explain himself;" odors readily differentiated but rarely named, yet false prompting is rejected, whilst correct is at once accepted. Vision: right 6/10, left 6/10; no hemianopia; intense papilledema, right swelling 8D, left 10D; numerous retinal hemorrhages especially in left; coarse nystagmoid jerkings of eyes on conjugate deviation to right; definite weakness of right lower facial muscles, most evident in emotional expression; no loss of power in limbs, but marked tremor in right hand; reflexes normal, except right abdominal reflexes; depressed; sensory system normal. Sudden attacks in which the patient seemed dazed and only remotely conscious were many times observed; in only one were there motor symptoms—a series of rapid movements of alternate flexion and extension at the right elbow-joint, neither associated with paresthesiæ nor followed by weakness.

A large cystic glioma mainly subcortical but reaching the surface in the middle third of the middle temporal convolution on the left side, was removed. Word-forgetfulness was subsequently greatly increased, and was still very evident on patient's discharge two months later.

Pathological Report.—Tumor weight 65 gm.; center consisted of organized blood-clot. Blood-supply contained in vascular spaces and embryonic vessels; very cellular, nuclei mainly peripheral; stroma scanty, glioma.

CASE 6.—*History.*—T. S. F., male, aged 35, was admitted in May, 1908. In the winter of 1906-1907 he became sleepless and irritable and was conscious of a gradual loss of memory. He was moody and suspicious, and for a short time was troubled by a sense of being persecuted; unsteadiness in walking and weakness with clumsiness of the right upper limb gradually developed, so that although he continued to work his usefulness was much diminished. In the summer of 1907 he often "looked dazed and lost," felt faint, and had weakness and tremor of the right arm and of both legs, especially the left, but never paresthesias. In November he was noticed often to have difficulty in finding words, but his articulation was unimpaired. During November and December he frequently vomited but afterward he never suffered even from nausea.

Examination.—Attention very variable; patient recognized and appreciated the use of objects, usually without being able to name them correctly; tendency to reiteration of the same verbal error; no word-deafness; on command, patient could select one of the several objects displayed and could correctly perform simple tasks. Patient could not name odors but could distinguish one volatile substance from another and alleged he recognized each. Taste normal. Vision right 6/8, left 6/18; bilateral papilledema, right + 5D, left + 6D; the swelling more recent in right; no hemianopia. Right deafness—neither bone nor air conduction; tympanic membranes normal. Other cranial nerves unaffected. No sensory loss. No sphincter disturbance. No weakness or ataxia in the limbs, but patient stood solely on his heels and when unsupported staggered straight backward. On extension of right upper limb coarse tremor appeared in hand; right knee- and ankle-jerks greater than left; both plantars of flexor type.

Operation.—A hard, light yellow, deeply subcortical tumor about the size and shape of a golf-ball was found in the left temporosphenoidal region; its removal was performed in two stages. Weight of growth 65 gm. A columnar-celled carcinoma.

CASE 7.—*History.*—H. G., male, aged 40, admitted July 31, 1908, on May 8, suddenly had a sensation as of "a vapor in the mouth, like the smell of smoke of coarse tobacco from a foul pipe," and lost consciousness for fifteen minutes. On recovering, he apparently understood all that was said to him, but until the following day he could not speak intelligibly. Subsequently for several days he had headache, weakness and numbness in the left arm and leg, and for three weeks felt too feeble to work. In June and July similar attacks preceded by the same aura and followed by a similar grave difficulty in expressing his thoughts, frequently recurred. In June his gait became unsteady, and "pins and

needles" sensation arose in both legs. From July 12 he had severe constant headache and marked failure of memory and attention. He never had sphincter trouble.

Examination.—Attention poor; memory for events good; marked word-forgetfulness; elliptical speech; tendency to recurrence of same verbal errors; instant and spontaneous recognition of mistakes; no word-deafness; articulation good. On admission no swelling of optic disks; some distention of fundal veins; ten days later slight swelling of left disk. Supranuclear type of weakness of right lower facial muscles; weakness of right upper extremity without spasticity. Lower extremities; no loss of power; on standing, patient staggered backward on heels, the toes being strongly dorsiflexed; no sensory changes; deep reflexes all brisk and equal; right abdominal, diminished and easily fatigued; left, active

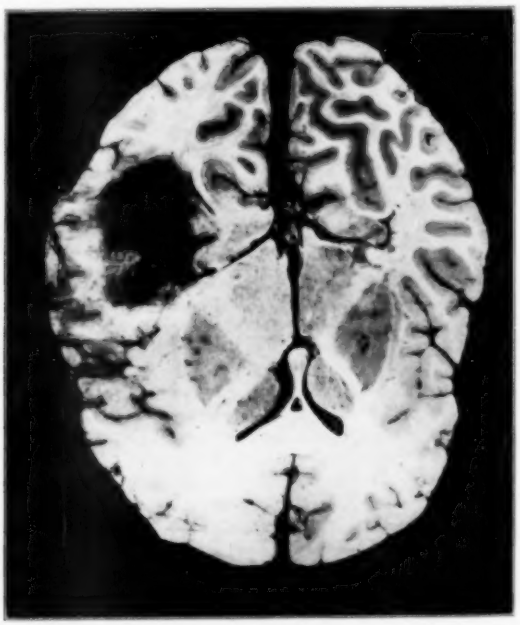

Fig. 4.—Brain of Patient 9. Left temporosphenoidal tumor. Horizontal section through basal ganglia.

and persistent. Plantars both flexor. August 28, occasional right, extensor, left always flexor.

Operation.—This displayed a large diffuse and irremovable growth, apparently of malignant nature, deeply situated in the posterior and upper parts of the left temporosphenoidal lobe.

Operation well sustained.

CASE 8.—*History.*—R. F., female, aged 35, admitted Nov. 19, 1909, from 1907, had frequent general epileptic fits, often associated with severe headache and vomiting. Almost all attacks were prefaced by a subjective sensation of smell and taste "like rotten fish," and less often by "a sound like some one singing," and were usually followed by marked difficulty in the recollection of words, and

consequent difficulty in speech. Memory much worse from January, 1909, and from October vision seriously deteriorated.

Examination.—Memory deficient; mental processes slow. Hearing better on left than on right side.

Taste and smell normal; vision, right 6/24, left 6/12. Bilateral papilledema. Highest point on right: + 3.5D., on left + 3.5D. (mydriasis incomplete on left). Retinal stippling on left more than right. Marked weakness of right lower face, especially evident on emotional movement. Motor and sensory systems normal.

Abdominal reflexes not obtained. Other reflexes normal.

Operation.—Nov. 30, 1909: A bone defect was made in left temporal region. Intracranial pressure was found to be greatly increased. A week later, the dura was opened over the upper border of superior temporal gyrus; the subjacent

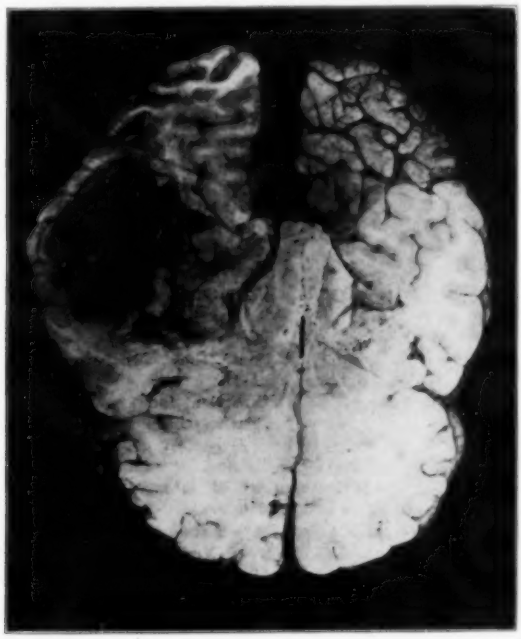

Fig. 5.—Brain of Patient 9. Section below basal ganglia.

cortex instantly bulged through the dural incision, and burst a few seconds later, emitting a jet of yellowish fluid. Exploration of the cavity thus opened proved it to be merely the dilated lateral ventricle, from which was removed a small hard tumor, growing from the choroid plexus and adherent to the tapetal margin.

Postoperative History.—For two days patient had no postoperative symptoms and no increased difficulty in speech.

Dec. 2, 1909: Patient in good general health, but completely unable to express her thoughts; words were slowly and distinctly uttered, but were quite inapt and without meaning; her errors caused patient much distress. Commands were perfectly understood and performed.

Dec. 13, 1909: Patient in excellent health. Vision, right 6/9, left 6/6; marked subsidence of optic disk swelling. Right facial weakness much diminished. No paresis of the limbs. Word-forgetfulness only rarely present. No apraxia. No attacks of crude sensations.

Jan. 14, 1910: Patient left hospital without symptoms.

CASE 9.—*History.*—J. M. C., female, aged 33, was admitted on May 14, 1909. May, 1904, she had a sudden attack of unconsciousness with general convulsions, in which her tongue was bitten. She was subsequently quite well till November, 1907, when she had another fit of sudden unconsciousness but without involuntary movements. April, 1908, she began to complain of nausea but vomited only once. In May, 1908, headache developed and gradually became more constant and severe; from the same time she often found she could not accurately name familiar objects; she would, for example, in these transient periods of word-forgetfulness call a clock "a watch," etc., but she was always at once aware of her mistake; from this date also she was subject to momentary losses of consciousness. From December, 1908, she was unfit to work; she did any task very slowly, was easily tired, spoke seldom and hesitatingly as if at a loss for words, but her articulation was unaffected. From March, 1909, her vision which had then been slightly defective for nine months became rapidly worse, and transient diplopia, and brief spells of blindness often occurred. For several months before admission she frequently "had a bad taste in the mouth" which rarely was followed by loss of consciousness.

Examination.—Attention and memory poor; mental processes slow but clear; marked word-forgetfulness with perfect articulation, but halting elliptical figurative speech; cranial nerves normal except for intense swelling of both optic disks; motor and sensory systems normal; gait and reflexes unchanged.

On the evening of May 16, coma suddenly supervened; a decompressive operation was at once performed over the left temporal region, but patient died two hours later.

Necropsy.—Left temporosphenoidal lobe considerably enlarged; slight pressure on left third nerve and left optic tract. Soft infiltrating tumor containing recent hemorrhages, extending throughout the center part of left temporosphenoidal lobe for 6 cm. in anteroposterior direction, forward to 1 inch from tip of the lobe, inward to posterior wall of descending horn of lateral ventricle, downward to margin of cortical gray matter.

Section through middle of basal ganglia and internal capsule. Tumor, limited on anteromesial aspect by posterior part of internal capsule, lay completely behind posterior limb of Marie's "quadrilateral."

Mesial surface merged with area of optic radiations. Microscopically: Sarcoma.

52 West Fifty-Third Street.

FURTHER EXPERIENCE IN THE PREVENTIVE TREATMENT OF RABIES WITH UNCHANGED VIRUS FIXE

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In a previous article,[1] I reported the result of treatment with unchanged *virus fixe* in forty cases. Review of the literature on this subject shows that the ultimate result of the preventive treatment is best when the least changed *virus fixe* is used.

Regardless of the good results from the exclusive use of unchanged *virus fixe* obtained by Ferran and myself, no other Pasteur institute has exclusively adopted this method. The aversion to producing experimental rabies by using unchanged *virus fixe* only, is not yet overcome.

In my first paper I stated that Ferran was of the opinion that one injection would give complete immunity.

In my first series of forty cases the patients were treated with doses fifty times larger than given by Ferran. The first ten patients were given two injections daily, eleven, one injection daily for ten days, and the remaining nineteen were given one injection daily for six days. The results by this method being very satisfactory, I made a further reduction. I decreased the time to one injection daily for five days and also gave smaller doses.

I hope the following report of ninety-two cases in which the patients were treated exclusively with unchanged *virus fixe*, will lead to the conviction of the innoxiousness of this method.

For the treatment I use exclusively the brain of rabbits infected with *virus fixe*.[2] The brain is removed and divided into hemispheres and each preserved on 50 per cent. glycerin slant agar in tubes 15 by 3 cm. (Figure 1). The tubes are then covered with a rubber cap to prevent evaporation and are kept in the refrigerator. This preserving method is preferable to glycerin water, being ready for use at all times and any bacterial contamination will be detected by growth on the surface of the agar.

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1. Proescher, Frederic: A Danger-free Method of Using Freshly Prepared Virus (*Virus Fixe*) from the Brain of the Hydrophobic Rabbit, New York Med. Jour., 1909, xc, 688.

2. The rabbits which are used for obtaining the *virus fixe* are killed during the paralytic stage by bleeding from the inguinal artery about twenty-four hours before the time death is expected. This method is preferable to spontaneous death because a certain amount of bacteria will enter the blood-stream during the agony and the brain will not always be sterile.

As a routine measure we use a fresh rabbit brain each week, although the *virus fixe* preserved in these tubes retains its virulence from four to six weeks. For obtaining a uniform amount of brain substance we use a urethral forceps with a concave alligator jaw which, when closed, forms a small cavity which will contain an average amount of 0.10 gm. to 0.12 gm. of brain tissue (Figure 2). The sterilized instrument is opened, forced into the brain substance (Figure 3), closed and removed and the contents deposited in a sterile glass. This amount is then thoroughly emulsified with a sterile glass rod, a few drops of salt solution added until a homogeneous suspension is obtained, and is further diluted with 30 c.c. of salt solution.

Fig. 1.—Brain substance preserved on 50 per cent. glycerin slant agar.

Three c.c. of this emulsion, which is equal to about 0.01 gm. *virus fixe*, is injected subcutaneously. The abdominal region is preferred.

In Table 1 my cases are grouped after the example of Pasteur, with the addition of one group in which the diagnosis is made by histological examination.

Group A contains such cases as were proved positive rabies by animal inoculation.

Group B contains cases which were diagnosed by competent veterinary surgeons.

Group C contains cases of suspected rabies, the animals, however, not having been examined.

Group D are cases diagnosed by histological examinations.

TABLE 1.—CASES OF RABIES GROUPED ACCORDING TO EXAMINATION

Group	Head and Face	Upper Extremities	Trunk	Lower Extremities	Contact Only	Total
A	2	13	0	5	1	21
B	0	2	0	0	2	4
C	6	8	1	7	0	22
D	4	23	0	17	1	45
						92

In these ninety-two cases, eighty-two patients were bitten by dogs, three were in contact only, four were bitten by horses, one in contact only, and two were bitten by a cat.

Twenty-three of these patients were females ranging in age from 3½ to 60 years, and sixty-nine were males aged from 17 months to 72 years.

Table 2 shows the length of time which elapsed between the time of bite and the beginning of treatment.

TABLE 2.—LENGTH OF PERIOD BETWEEN TIME OF BITE AND BEGINNING OF TREATMENT

Time	Cases
1 to 3 days	56
4 to 7 days	19
8 to 14 days	13
15 to 31 days	3
37 days	1

In some of these cases the wound had been cauterized previous to admission, but in no case was the cauterization sufficient to destroy the virus.

The ninety-two cases in which this treatment was used show that the preventive treatment with unchanged *virus fixe* gives constant results, regardless of the decreased doses and the time of treatment.

When we consider that in other Pasteur institutes, which use the old or a more or less modified scheme of treatment by Pasteur, that the average mortality is between 0.12 and 1.28 per cent. and further that it is shown by the statistics collected by Diatroptoff that the mortality is increased with the length of time between the bite and the beginning of the treatment, the entire use of unchanged *virus fixe* is without doubt superior to the other methods.

TABLE 3.—DEATHS UNDER TREATMENT WITH VIRUS FIXE

Beginning of treatment after the bite	Cases, No.	Deaths, No.	Per Cent.
1 week	4602	26	0.56
2 weeks	961	16	1.66
3 weeks	313	10	3.19

In none of my cases has an ill effect occurred which could be traced to the use of unchanged *virus fixe*.

If it is possible to immunize animals with one injection of unchanged *virus fixe,* why not human beings? According to my practical experience with human beings, I gave large doses of unchanged *virus fixe* without danger. Therefore I conclude that one large dose of fresh *virus fixe* should give complete immunity.

By the present treatment, I give 0.05 gm. in five days. My first forty cases I gave 0.4 gm. daily or 2.4 gm. in six days. One dose of 0.1 to 0.2 gm. should give a complete protection even in the more extensive bites.

Fig. 2.—Urethral forceps with concave alligator jaw.

Ferran gives 0.3 gm. of fresh *virus fixe* in five days, which is probably too high since he uses only the superadjacent fluid and not the sediment. The average amount would be about 0.15 gm.

Fig. 3.—Cutting brain substance with urethral forceps.

I agree with Marx that one injection will immunize all human beings capable of being immunized, and that more or less duration of the incubation time need not be considered, because an incubation time of twelve days has not been definitely determined in human beings. Immunity will be produced within the limits of this time.

The danger of an intoxication from the rabies toxin, the last objection of Marx, is without foundation because the entire amount of 0.1 to 0.15 gm. is about one-fourth smaller than the first dose given to the first forty patients and without any symptoms.

Theoretically and practically, there is no objection to giving one large dose of unchanged *virus fixe*, both as to safety and immunity. For rapid and intensive absorption, it is advisable to inject the dose in three or four different locations.

To say that mortality is reduced to the minimum by the exclusive use of unchanged *virus fixe* will have to be confirmed by use in a larger number of cases.

The paralytic symptoms observed during or after treatment with the other methods seem to be due to an abortive form of street virus infection, probably due to an incomplete immunity and not to the treatment with *virus fixe*.

It is necessary to keep in mind that not all the different strains of *virus fixe* in unchanged condition which are used in other institutes are entirely free from danger to human beings. Every other *virus fixe* which will be used in unchanged condition must be carefully tested before using on human beings. It is probable, however, that all the *virus fixe* is more or less avirulent to human beings, as has been shown by many careful investigators.

The question arises: Can we further decrease the time of treatment without risk? I believe this question can be answered satisfactorily.

Marx showed experimentally that rabbits after one injection intraperitoneally with unchanged *virus fixe* can be completely immunized. The rabbits after the twelfth day are completely immune to intracranial infection. I can confirm Marx' experiments.

By the old Pasteur method and its modifications in which unchanged *virus fixe* is not given at all, there is only a very small amount of virulent *virus fixe* in the dried spinal cord which will give immunity. Also a very small amount of unchanged *virus fixe* is given by the Högyes dilution method. It is evident that the whole amount of *virus fixe* which is given in from eighteen to twenty-one days by the old scheme, could be reduced to one or two injections with unchanged *virus fixe*.

What rôle the toxins play in the immunization I leave undecided. Their existence is not evident, and in my opinion they are without great value for the immunization.

The experience with other vaccines has demonstrated that a certain percentage of cases, in spite of the same conditions, cannot be immunized or, better said, that the immunity cannot be produced to such a point that a complete protection is assured. We have also to count on a certain amount of failure, in spite of using the most intensive treatment.

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A CONSIDERATION OF SOME CHEMICAL TRANSFORMATIONS OF PROTEINS AND THEIR POSSIBLE BEARING ON PROBLEMS IN PATHOLOGY *

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Recent investigations concerning the structure of proteins have led to a readjustment of our ideas with respect to the manner in which these substances may become an integral part of the organism; and the study of the changes which occur from the time when protein has been built up into cell structure until its exit from the body in the form of waste products is at present only in its infancy. According to the newer conception, the protein molecule is a huge complex consisting of the union of a large number of simple amino-acids. This conception is due largely to the researches of Emil Fischer, who has succeeded in fastening together various combinations of amino-acids in such a manner that the resulting compound behaves in some respects like certain of the proteins. Some of these substances, called polypeptids, have indeed been isolated from the decomposition of native protein. According to Fischer, proteins are merely mixtures of complex polypeptids and cannot be considered as chemical individuals. This view, however, is not shared by other protein chemists.

In its passage through the alimentary canal the large protein complex undergoes a degradation,—a transformation into simpler molecules which are still regarded as simple proteins, together with a long chain of amino-acids belonging to the aliphatic, aromatic and heterocyclic series. Our modern view of the nature of protein forbids the acceptance of the older idea that the necessity for alimentary treatment of protein is merely to transform protein into a condition suitable for absorption. Obviously, solubility and diffusibility are only a small portion of the process; otherwise it would be unnecessary to entail so much labor on the gastro-enteric tract by the apparently needless formation of amino-acids. The need for nitrogenous substances is to replace cellular structures worn out through metabolic activities. Just how this replacement occurs is problematical. Certain it is that the only detectable nitrogenous food supply for such structures is to be found in the proteins of the blood. No amino-acids or other protein decomposition products have been isolated from the

* The Middleton Goldsmith Lecture for 1911; read before the New York Pathological Society at the Academy of Medicine, March 18, 1911.

blood.[71, 2] An explanation for the necessity for the extensive disintegration of the protein molecule has been offered as follows:

> "Every species of animal—in fact, every individual—has its specifically constituted tissues and cells. If the diet were always the same, the formation of the tissues might bear some close relation to the components of the food. The diet varies, however, and, especially in the case of human beings and the omnivora, is exceedingly diverse in nature and to make its organism independent of the outer world in the matter of food taken, it disintegrates the nutrient it receives, and utilizes those components which may be of service to it in building up new complexes."[1]

Many important functions have been attributed to the intestinal wall, but perhaps none of more significance than a selective power for the synthesis of amino-acids into serum albumins. According to this view, the intestine receives a series of more or less simple amino-acids and by uniting them in varying proportions forms definite compounds, probably serum proteins, to meet the organism's requirements. The serum proteins are then drawn on to furnish nitrogen requirements for the specific organ or group of cells. This probably entails a further transformation. Such a theory accounts for the necessity of the complete degradation of protein in the gastro-enteric canal and accords with the entire absence of cleavage products in the blood. On the other hand, this extensive degradation, synthesis and further disintegration appears quite uneconomical physiologically. In the first place, only a comparatively small amount of nitrogen is needed to rebuild tissue, and the excess must be transformed into some form easy of elimination, all of which entails loss of energy and tissue waste. It is a matter of common observation that when protein is fed, practically all the nitrogen is rapidly excreted, and one is inclined strongly to believe that this portion has never been re-synthesized into protein. If amino-acids or other decomposition products could be found in the blood, the solution of the problem would be at hand. The failure to discover them does not disprove their presence, however, since the quantity in the portal vein, at any one moment, may be so small as to escape detection with our present methods.

Whichever way one views this problem, the fact remains that sooner or later intermediary processes must be concerned, primarily with a series of amino-acids. These are the substances that must be metabolized in either case, and it is to some of the transformations that these compounds may undergo within the organism that I particularly desire to call attention. It is my purpose to indicate the possible bearing of certain types of intermediary processes upon problems in pathology, for it is my belief that the hope for a complete understanding of some of the phases of disease will be realized in proportion as our knowledge of intermediary processes increases.

DEAMINATION AND THE SIGNIFICANCE OF AMMONIA IN THE BODY

Modern investigations teach that when amino-acids obtain entrance to the tissues, a process of deamination rapidly occurs; the nitrogen is split off in the form of ammonia. In other words, the amino-acid is converted into a nitrogenous and a non-nitrogenous portion. It is probable that this process of deamination takes place for the most part in the liver, although the liver is by no means the only organ capable of performing this reaction, as has been pointed out by Jacoby[51] and Lang.[57] The older observation of Nenki, that blood flowing from the intestine is richer in ammonia than the blood of any other vessel, may also be regarded as probably our first indication that the intestinal wall may carry out the process of deamination. Ordinarily, the ammonia split off reappears in the urine as urea, being synthesized into this closely related compound in the liver. That deamination occurs also with certain protein complexes, has been conclusively demonstrated by Cohnheim.[24] The further transformation of the non-nitrogenous part will be considered later.

Under normal conditions the quantity of ammonia excreted in the urine varies within certain well defined limits, and in general is directly proportional to the intake and total output of nitrogen. The elimination of ammonia in disease may vary enormously, and usually when a changed excretion is observed it is in the direction of a greatly increased output. In fact, ammonia output in the urine is probably more easily affected than the elimination of any other single urinary constituent, except the excretion of urea which bears a reciprocal relation to ammonia. If the literature relating to ammonia output in disease is reviewed, it is found that increased ammonia excretion[77] is characteristic of pathological conditions apparently widely diverse in nature. For instance, an augmented ammonia output has been observed in cholera, intestinal hepatitis, carcinoma of the liver, cirrhosis of the liver, pneumonia, polyarthritis, typhoid, various other fevers, acute uremia, phosphorus poisoning, gastro-enteritis, starvation, diabetes, pernicious vomiting of pregnancy, eclampsia, etc.

Ammonia in the normal urine is looked on to-day as an index to the quantity of acids present. Acids are toxic to the organism, as has been demonstrated repeatedly, and ammonia is diverted from its transformation into urea to neutralize these acid radicles.[42, 44, 25, 31, 52] The same idea prevails with respect to diseased conditions in which increased ammonia in the blood and urine is regarded as evidence of increased production of acid radicles.[77] It is a well-known observation that this excessive elimination may be greatly diminished by feeding other alkalies, as, for instance, in diabetes. If ammonia is employed in the tissues merely to neutralize acid radicles, it would seem fair to assume that if

sufficient alkali were introduced, no ammonia should appear in the urine. Experimentally, such a condition has never been brought about in spite of very large doses of alkali. From this fact it would appear that a certain quantity of ammonia is continually present in the blood. This holds true also for the herbivora, even though these animals are assumed to neutralize acid radicles by alkalies other than ammonia.

Throughout the literature relating to acidosis and ammonia excretion in the urine, emphasis is laid on acid radicles as toxic agents. Little or no attention has been devoted to the rôle which may be played by ammonia itself when viewed from the same standpoint. As a matter of fact, ammonia is exceedingly poisonous and few salts exceed those of the ammonium series in comparative toxicity. On the other hand, of the acid radicles which are supposed to exert such deleterious effects, as, for example, in diabetes, not one has been shown to have any strikingly toxic properties, at least in the normal organism. From these statements the possibility is offered that increased ammonia output in the urine may really mean increased ammonia production resulting from decreased urea formation. Experimentally, there is no evidence that such may not be the case, and according to this view ammonia must be neutralized, which would account for the presence of organic acids in the urine, as in diabetes, starvation, liver disorders, etc., precisely as the introduction of camphor, menthol, thymol, etc., accounts for the appearance of glycuronic acid in the urine. In this connection another interesting problem presents itself. In diabetes, beta-oxybutric acid is the acid formed in large quantity, whereas in other conditions, as in cirrhosis of the liver, lactic acid is found. As a rule, the two do not occur together except in starvation and in pathological conditions in which inanition is an accompaniment. The presence of these two compounds in the urine would indicate two different types of mechanism slightly diverted from the normal.[93] In entire accord with the theory that ammonia may be the toxic agent are the observations of Carlson[21] and Jacobson.[49] The former has shown an increased quantity of ammonia in the blood after complete thyroidectomy and parathyroidectomy. The latter has demonstrated that the concentration of ammonia in the blood necessary to produce experimental ammonia tetany is practically equal to that found during parathyroid tetany. "This supports the view that the increased ammonia in the blood of parathyroidectomized animals is directly responsible for the tetany and the depressive symptoms."[49]

If, on the assumption that a common law underlies all the various pathological conditions mentioned, one attempts to account for the presence of ammonia in the urine, the suggestion presents itself that it is in some way connected with the metabolism of the carbohydrates. In practically every condition in which ammonia in the urine is characteristic,

there is either a lack of carbohydrates, as in prolonged starvation, or a faulty utilization of carbohydrate, as in diabetes, cirrhosis of the liver, or after complete removal of the thyroids and parathyroids, etc.[92] It would appear, therefore that carbohydrate is the factor controlling the regulation of ammonia production.[93] Thus in prolonged starvation, ammonia in the urine may be greatly diminished by feeding carbohydrate.[77, 93] In the solution of the problem as to the part played by carbohydrate, at least two possibilities are presented: 1. Carbohydrate influences the output of ammonia indirectly by its effect on the combustion of fat, for it is well known that fat is burned much more readily when carbohydrate is present than when the store of this substance in the body is greatly depleted. 2. It may be possible that the liver cell, for instance, is incapable of effecting urea synthesis in the presence of insufficient carbohydrate in that organ. The latter hypothesis certainly presents interesting problems, both for the physiologist and for the pathologist. Attempts have been made in our laboratory to follow this hypothesis to its logical conclusion. The results thus far obtained, however, have not been far-reaching for the reason that it is exceedingly difficult to obtain the proper experimental conditions. The investigation has been carried out on animals entirely. In the first place, an endeavor has been made to remove the carbohydrate store from the animal's body by various means with the hope of inducing increased ammonia in the urine. Prolonged starvation, phosphorus poisoning, a combination of the two, phloridzin intoxication alone and together with prolonged inanition, and cocain poisoning have proved unsuccessful in inducing increased output of ammonia. This result is in harmony with those obtained by other investigators (Jackson and Pearce,[48] Richards and Wallace,[83] Underhill and Kleiner[94]). These facts by no means invalidate the hypothesis, for it is well known from the researches of Pflüger and his pupils that it is exceedingly difficult to get dogs glycogen-free. Since it is well known that dogs are refractory in this respect, inanition experiments were carried out also with the pig and rat, omnivora, and hence, presumably, allied to man in metabolism. The results were in entire accord with those with the dog. Ammonia in the urine was not increased. From this point of view it seems most probable that the decision of this question can be obtained most readily with the human subject.

If ammonia is to be regarded merely as an alkali for neutralization purposes, rather than as a toxic agent *per se*, it may be cited as a splendid illustration of the "factor of safety" principle enunciated by Meltzer[67] for other mechanisms. Ordinarily, ammonia is transformed to urea, but if acid radicles are floating in the body fluids they are rendered inert by union with ammonia, hence less urea is formed. Therefore, increased ammonia in the urine, with a corresponding diminution in the urea may

be regarded as an indication that the body is endeavoring to maintain normal conditions and not that there is necessarily any inability to form urea on the part of the organism, or that lesions in one or another organ are necessarily related to increased ammonia output. Indeed, even when acute yellow atrophy of the liver is at its height, the quantity of ammonia in the urine may be normal.[77]

Closely associated with problems concerning the significance of ammonia, are those having to do with the relation of this substance to the amino-acids and the mechanism of deamination. Within the last few years discussion of the relation of so-called defective or insufficient deamination in a series of pathological conditions has come into vogue. It has been assumed that the liver was incapable of performing its function and that the condition was indicated by high ammonia and a high undetermined nitrogen in the urine. It does not seem to have occurred to those who advocate this point of view that high ammonia and the presence of amino-acids in the urine present incongruous conceptions if the sum of urea and ammonia nitrogen is normal. In other words, if deamination were defective, one would expect low ammonia in the urine when amino-acids are present. Much stress has been laid latterly on the occurrence of amino-acids in the urine. In health a little glycocoll has been isolated in the urine, which is not strange when one considers the rôle of glycocoll as a compound intended to render toxic substances innocuous as in the case of benzoic acid, and the comparative difficulty with which glycocoll is burned. Leucin and tyrosin have been isolated from the urine of patients with acute yellow atrophy, and with phosphorus poisoning.[75]

According to Ignatowski,[47, 4, 23, 34, 104, 88, 41, 65, 78] glycocoll, leucin, tyrosin and aspartic acid are found in pneumonia and leukemia. Similar finds are obtained in scarlatina and typhoid.[50, 39] Insults to the pancreas[17] may lead to the excretion of a polypeptid which on hydrolysis yields tyrosin, and according to several observers[70, 2] a similar compound may be obtained from diabetic urines. As a result of disturbed metabolism induced by lack of oxygen,[61, 62] amino-acids may appear in the urine as well as after ether-chloroform narcosis.[5] These bodies may also be present in exudates and in the fluids formed in edema.[76, 75]

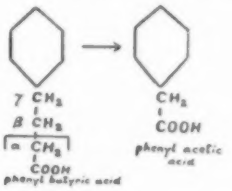
To account for the presence of amino-acids in the blood and hence also their excretion by the kidney, it is unnecessary to assume that defective deamination is responsible. They may be produced, as for example, by increased autolysis of a tissue or organ in a part of the body far remote from the organ or organs possessing the power of deamination and may therefore be eliminated through the urine before the organs of deamination have had an opportunity of performing their function. In other words, these compounds may be formed in the muscles, for instance, and be eliminated in a large part by the kidney before the liver, which may be

cited as an organ of deamination, has had an opportunity of acting on them. In harmony with this idea may be cited the conditions which obtain in this respect in cystinuria.[75] In certain of these patients, the amino-acid, cystin, is eliminated through the urine either alone or in company with other amino-acids, for example, leucin and tyrosin. Apparently, the cystinuric patient is incapable of deaminating and burning the cystin. Nevertheless, when cystin[11, 102] is fed to such individuals they experience no difficulty in completely deaminating and burning this amino-acid, and it has also been demonstrated that certain, at least of the cystinurics, can handle other amino-acids, as tyrosin[90] and aspartic acid,[103] when fed. The reason for the presence of amino-acids in the urine under the pathological conditions previously cited, may be similar to that frequently given for cystinuria, namely, that the cystin eliminated arises as a result of processes within the organism, not necessarily from the food. And in neither case is it necesary to assume defective deamination.

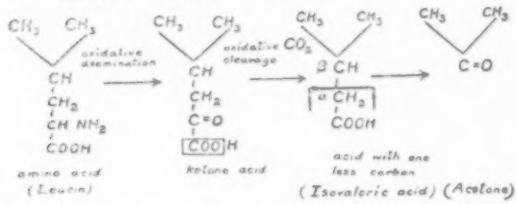
THE FURTHER FATE OF AMINO-ACIDS

Until recently our knowledge concerning the exact mode of decomposition of the cleavage products of protein has been extremely limited. It has been assumed for years that the non-nitrogenous portion of the amino-acid is oxidized and hence may be looked on either as a direct source of energy, or as potential energy residing in carbohydrates or fats synthesized from such material. Recent observations, however, have tended to give us a more enlightened view as to the exact way in which these amino-acids are handled. Thus, from the investigations of Emden, Salomon and Schmidt,[35] it may be seen that leucin added to the blood of a dog and made to pass through the surviving liver causes a considerable increase in the acetone contained in the circulating blood. Under normal conditions some acetone is a product of liver activity.[53]

In order to understand the steps necessary for the production of acetone from leucin, certain other facts must be taken into consideration. Knoop[53] has conclusively demonstrated that the aromatic fatty acids are decomposed in the body in such way that there is an oxidation at the beta carbon atom followed by a cleavage in the side chain between the alpha and beta carbon atoms. Thus, phenylbutyric acid is decomposed into acetic acid and phenylacetic acid. The latter appears in the urine, and the acetic acid is presumably decomposed to CO_2 and H_2O.

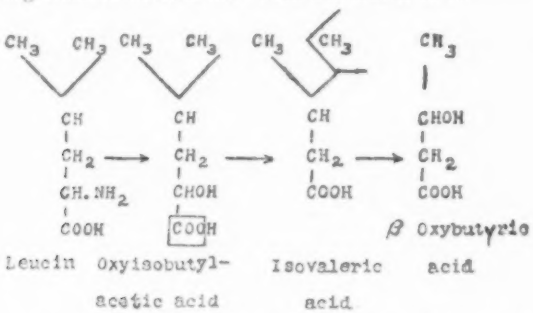


It is perfectly possible that the breaking down of the aliphatic fatty acids takes place in somewhat the same fashion. Reasoning from this viewpoint it is probable that the transformations which occur in the production of acetone from leucin are as follows:



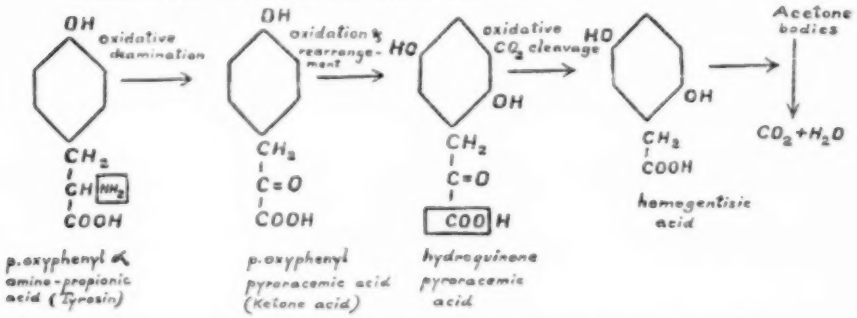
Leucin first undergoes oxidative deamination by which a ketone acid is formed. Then by oxidative CO_2 cleavage isovaleric acid is produced. Next cleavage takes place between the alpha and beta carbon atoms.

On the other hand, Baer and Blum[12] have found an increased output of beta oxybutyric acid in the urine after giving leucin to a diabetic and the following transformations have been attributed to it.

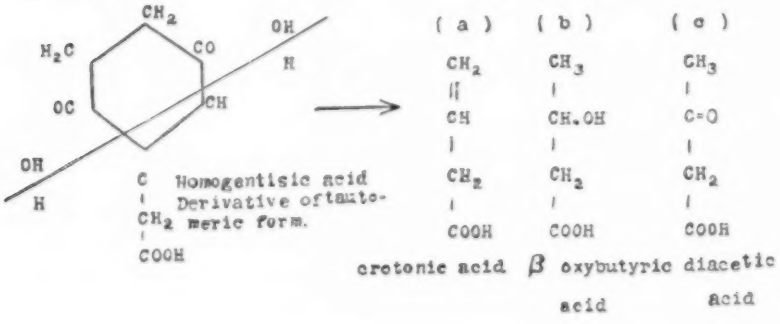


Whether one can assume from these observations that the organism of the diabetic is incapable of handling the amino-acid in a normal manner remains a problem for future investigation to decide. "With the proof of acetone formation from products obtained from protein derivatives, we obtain for the first time a clear idea concerning the utilization of the carbon chains free from nitrogen from certain amino-acids. We learn in this way to consider the formation of acetone as a normal process, it being a normal product in the decomposition of leucin."[1] If acetone is a step in the demolition of certain of the amino-acids, why is it that in various pathological conditions, as diabetes, gastro-enteritis, starvation, etc., large quantities of this substance are excreted in the urine instead of being further decomposed as in health? In answer to this query, it may be stated that probably only a small portion of the acetone excreted under the conditions just cited really has an origin in the carbon-free rest of the amino-acids.

When a fatty acid attached to the benzene ring is followed through the organism, the changes which occur are not quite so simple.[1, 26] Ordinarily, when fed to the normal organism, tyrosin, which is such a combination, entirely fails of detection in the excreta. Not only has the fatty acid been decomposed, but the benzene ring has been broken, which may be regarded as a difficult chemical reaction. The possible steps through which tyrosin must be carried have been indicated by Neubauer.[74] There is a class of pathological subjects that present certain anomalies in metabolism. These subjects, alkaptonurics, excrete urine containing homogentisic acid.[75] For a long time it has been recognized that tyrosin fed to the alkaptonuric results in an increased output of homogentisic acid. Ordinarily, this substance is decomposed in the organism, but in the class of individuals referred to, it would appear that this decomposition is withheld or inhibited. The changes which lead to the formation of homogentisic acid in the alkaptonuric and hence probably also in the normal subject have been outlined as follows:



In harmony with the idea that homogentisic acid is an intermediary product in the decomposition of tyrosin is the demonstration that the normal liver is capable of forming acetone from homogentisic acid.[35] The reactions which occur are probably in accord with the suggestion given below:



So far as the condition of alkaptonuria itself is concerned, it can hardly be looked on as distinctly a pathological state; it is rather an anomaly of metabolism. Nevertheless, it is possible that it may bear a relation to disease. Thus, it has been suggested that there is an as yet unexplained relationship between alkaptonuria and chronic polyarthitis.[32, 58, 79, 74] Homogentisic acid is also closely related to certain pigments which occur under abnormal conditions. It may be easily transformed into a dark-colored pigment which bears a relation to the group of bodies known as melanins which are also protein derivatives. Whether homogentisic acid is concerned in the production of color in melanotic tumors, remains a question for future decision. It has been suggested[10] that there is relationship between homogentisic acid and the coloring of the bones in ochronosis and at times ochronosis and alkaptonuria occur simultaneously.[59]

If it can be demonstrated that alkaptonuria bears a direct relationship to certain diseases, it is obvious that the complete understanding of the chemical transformations which lead to the production of this anomaly will undoubtedly prove of value in the unraveling of other abnormal processes.

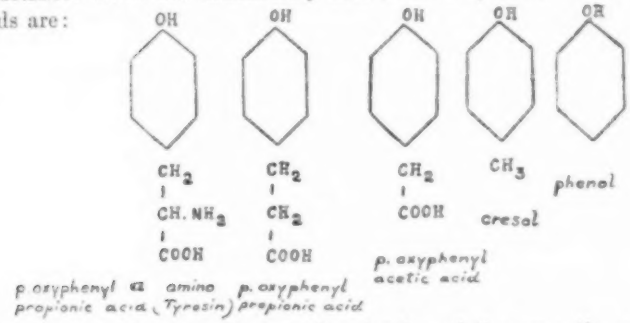
According to the views which have just been expressed concerning the fate of amino-acids in the body, the non-nitrogenous portion is merely broken down into simpler compounds and eliminated. This process of degradation undoubtedly furnishes a certain amount of energy in the form of heat. Looked at from another point of view,[64] the non-nitrogenous part of certain, at least, of the amino-acids may be synthesized to carbohydrate and fat which in turn are utilized as sources of energy.

Thus far, the whole question as to the fate of amino-acids in the body has been looked on as one of analysis or demolition. Recently it has been suggested that there may be a synthesis of amino-acids within the organism, and Knoop[54] has placed on record certain experiments which tend to substantiate this view. Thus, after feeding phenyl ketonebutyric acid or even oxyacids of a similar type, he was able to separate from the urine an acetyl derivative of an amino-acid. Here, for the first time, there is established a direct relationship between protein and carbohydrate metabolism.

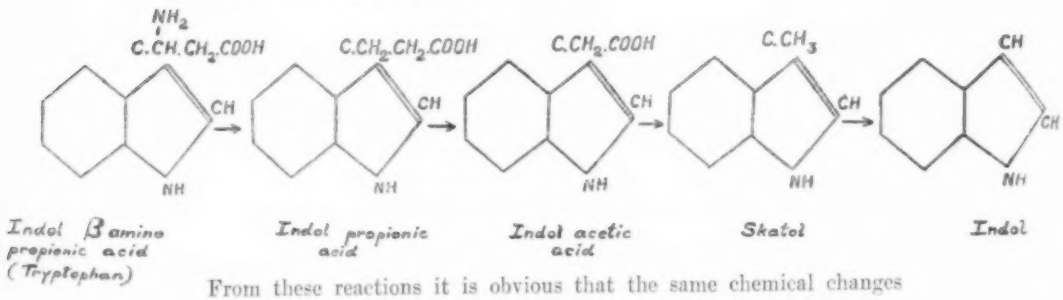
BACTERIAL PRODUCTS

Indol, Skatol, etc.—As a result of the bacterial digestion of protein, certain well-known and well-defined products have been isolated and their specific influence on the organism noted. Not only have these bodies been separated and identified but the chemical transformations leading to their formation have been made clear. The protein derivatives, tyrosin and tryptophan, are the mother substances for the best-known bacterial products. In the intestinal contents have been found a number

of substances which are undoubtedly derived from tyrosin. These compounds are:



According to these reactions, a deamination of the aromatic amino-acid must occur in the large intestine. The further reaction for the production of p. oxyphenylacetic acid involves the cleavage of carbon dioxid from the carboxylic group and subsequent oxidation of the carbon atom. If phenol is produced from cresol, then demethylation must occur. These reactions if correct, must involve the processes of deamination, cleavage of carbon dioxid, oxidation and demethylation. From tryptophan the following products are formed.

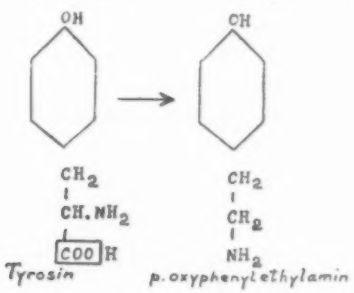


From these reactions it is obvious that the same chemical changes have occurred as in the transformations for tyrosin, namely, deamination, carbon dioxid cleavage, oxidation and finally demethylation. On the other hand, it has been suggested recently that indol may arise in part as a result of intermediary processes quite distinct from those involved in putrefaction.[16]

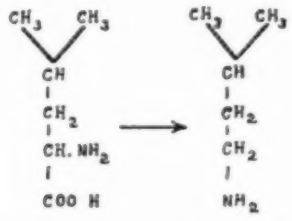
Ordinarily, when intestinal putrefaction is mentioned one invariably thinks of indol and skatol as being responsible for the series of disturbances which may be associated with this condition. It has been assumed that a long list of pathological conditions may be closely related to increased intestinal putrefaction. Thus, this condition has been held responsible in part for sciatica, tetany, epilepsy, eclampsia, many forms of dermatitis, cirrhosis, arteriosclerosis, various types of nervous diseases, chlorosis, myxedema, cretinism, pernicious anemia and nephritis.[98, 73]

Although there is abundant clinical evidence that excessive intestinal putrefaction may be associated with or responsible for marked disturbances, the substances thus far isolated from intestinal contents can not be said to possess very profound toxicity. It is true that indol when administered in quantities up to 2 gm. per day causes frontal headache, irritability, insomnia and confusion,[45] and it has been shown further that indol and skatol cause muscle to react to stimuli like fatigued muscles.[60] But the comparatively slight toxicity can hardly be responsible for some of the symptoms observed. Various explanations have been offered to account for the discrepancy noted between clinical evidence of intestinal intoxication and the fact that the substances formed thus far isolated are only slightly toxic. The most plausible explanation for the discrepancy mentioned is that the list of compounds which may be formed in putrefaction has not yet been exhausted, and it is possible, and indeed probable, that in time other compounds of putrefactive origin will be found that will adequately account for the clinical symptoms observed. On the other hand, it be possible that indol and skatol may exert quite different effects on the normal organism from those which it exerts on a body whose resistant powers have been lowered as a result of other pathological processes. In other words, the receptive condition of the body under the two conditions mentioned may be entirely different, producing in turn quite radically differing symptoms.

Amines and Their Formation.[13]—That we have by no means isolated all the active principles from putrefactive mixtures may be well illustrated by the investigations recorded during the last three years. In 1907 Dixon and Taylor[29] aroused considerable interest by the publication of their observation that alcoholic extracts of the human placenta when injected intravenously caused a marked rise in blood-pressure and contractions of the pregnant uterus. On repetition of this work, Rosenheim[87] failed to corroborate the findings of Dixon and Taylor when extracts of perfectly fresh placentas were employed. When, however, extracts of placentas in various stages of putrefaction were intravenously administered, results were obtained identical with those of Dixon and Taylor. A substance responsible for these effects has been separated and identified by Barger and Walpole,[15] according to whom the active principle is p. oxyphenylethylamin and may be derived from tyrosin as a result of the following reaction:



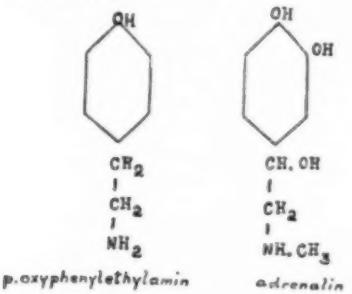
Moreover, iso-amylamin has been isolated from putrefactive mixtures probably being derived from leucin in accordance with the following reaction:



(Leucin) Isoamylamin

These results have led the authors to remark that they are induced "to emphasize the probability that the amins which we have isolated are normally formed by putrefaction in the intestine and are absorbed from it."[15]

The compound, p. oxyphenylethylamin, is of peculiar interest for several reasons. In the first place, it was originally isolated by Emerson[36] from an autolysis of pancreas and its mode of formation from tyrosin has always been considered unique. It is obvious at present that it was probably produced by putrefaction in this case also. Much more interest attaches to this substance from its great resemblance, both structurally and pharmacologically, to epinephrin.

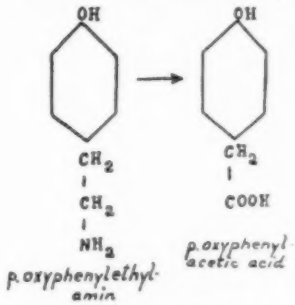


p.oxyphenylethylamin adrenalin

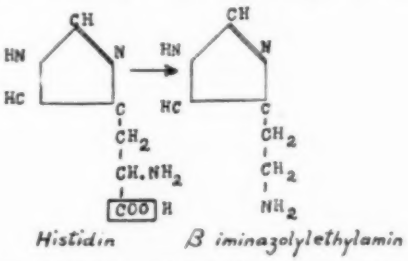
"P. oxyphenylethylamin has an action very similar to that of adrenalin [epinephrin], reproducing both the motor and inhibitory effects of nerves of the true sympathetic system. It produces the motor more powerfully than the inhibitory effects. Its action differs from that of adrenalin in being weaker, and slower in onset, and in being less strictly though mainly peripheral. It is absorbed from the subcutaneous tissues and the alimentary canal and produces its effects when so administered."[27] Isoamylamin has a similar action.

Finally, it is of exceeding great interest to note that p. oxyphenylethylamin is one of the substances which give to ergot[14] its characteristic

action on the uterus. It is also probable that it is identical with the urohypertensin of Abelous and Bardier.[6] These observations also indicate the necessity for controlling all possible sources of bacterial contamination when extracts of animal tissues are employed in demonstration of specific action. Again, "Many observations have been published recently concerning the presence in the blood-serum and urine in various pathological conditions, of substances which cause dilatation of the pupil of the enucleated eye of the frog. The fact that both these amins have this action casts some doubt at least on the validity of the assumption, made by certain observers, that the substance in serum, responsible for this effect, is adrenalin."[27] On introduction into the body, the base is eliminated as p. oxyphenylacetic acid,[40] another example of deamination.



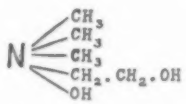
When histidin is subjected to the action of putrefactive bacteria, a compound[7] is produced which holds promise of being responsible in a measure for certain reactions which have long been unexplained.



This substance, beta-iminazolylethylamin, resembles in some respects p. oxyphenylethylamin in that both compounds are contained in ergot extracts, and both substances exert similar influences on the muscle of the uterus. In addition to the reactions possessed in common with p. oxyphenylethylamin, beta-iminazolylethylamin is capable of calling forth symptoms practically identical with those induced by injections of peptone solutions, or by serum or other protein in the sensitized guinea-pig, that is, producing anaphylactic shock.[27] The base has also a mild,

direct, stimulant effect on the activity of the salivary glands and the pancreas. This secretory action, being paralyzed by atropin, may be regarded as a weak action of the pilocarpin type; the association has some interest in that pilocarpin also contains an iminazole ring. More recently this base[28] has been isolated from extracts of the intestines, thus lending support to the suggestion that under normal conditions it may exert a more or less definite function in the maintenance of nutritional rhythm.

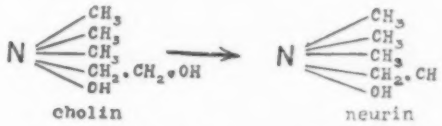
Closely associated with p. oxyphenylethylamin in extracts of placentas is another compound which may also be considered as an amin and which has an action antagonistic to that of p. oxyphenylethylamin. This compound, cholin, has been the subject of a great deal of discussion during



the last few years. It undoubtedly has its origin in a lipoid compound, lecithin, a constituent of practically all cells. It is, therefore, apparent that in putrefactive processes in the tissues, cholin may arise in relatively large quantity and, although not highly toxic when given by mouth, it may be exceedingly poisonous when allowed to come in contact with nervous tissue. Thus, Donath[30] observed severe tonic and clonic convulsions after cholin had been injected directly into the cortex or under the dura. This investigator offers the opinion that cholin may be responsible for epileptic convulsions—an opinion founded on the fact that he with other investigators[43, 86] has been able to demonstrate the presence of cholin in large quantities in the cerebrospinal fluid of epileptics and in other conditions associated with destruction of nervous tissue. In accordance with this idea, unsuccessful attempts[95] have been made to demonstrate the presence in the blood of cholin in animals during the tetanic convulsions caused by complete removal of thyroids and parathyroids. The removal of the glands has been shown to result in marked changes in certain areas of the nervous system,[97] and it was assumed that these histological changes were due to chemical reactions whereby cholin might be liberated and produce a secondary effect.

Chemically related to cholin is neurin, a substance easily formed from cholin by oxidation, which is nearly twenty times as toxic as the latter. The possibility presents itself that neurin may be formed from cholin within the organism under certain pathological conditions and may be responsible for some of the symptoms characteristic of certain abnormal conditions as salivation, vomiting, diarrhea and a specific action in causing arrest of respiration. This formation of neurin within the organism and any relationship which it may bear to deranged metabolism has never

been conclusively demonstrated. It has been shown, however, that neurin may be excreted, at times at least, through the urine.[56]



These compounds, together with muscarin and betain, constitute one of the groups of the ptomains, so-called, and hence heretofore have been interesting chiefly because of their advent into the organism through the introduction of decomposing tissue taken as food. Nevertheless, inasmuch as they arise outside the body as a result of putrefactive process, there remains open the possibility that they may be formed in the alimentary canal or in tissues either in a process of degeneration or putrefaction. The old idea, that there is a hard-and-fast line to be drawn between plant alkaloids and animal poisons is rapidly disappearing, and the fact that one toxic compound, as for instance muscarin, occurs as a rule in plant tissue does not exclude the possibility of the presence of the same body as a result of chemical reactions within the animal organism. The best recognition of this disappearing demarcation line is to be found in the new publication by Winterstein and Trier,[101] where all basic substances, whether of animal or plant origin, are considered as alkaloids.

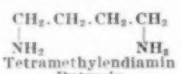
From this review of the more recently discovered compounds which may arise within the body by putrefactive processes, one fact stands forth with striking clearness, namely, the possible functions which some of these substances may exert in physiological processes and their significance in problems concerned with disease. We have seen that one compound resembles epinephrin, both structurally and in physiological activity, while another stimulates the activity called forth by pilocarpin. Epinephrin and pilocarpin are in daily use as drugs, the degree of whose activities may be regulated at will. The protein derivatives mentioned have practically similar actions but, as they arise within the organism, can not be subjected to voluntary control. It is likely that under normal conditions, only small quantities of these compounds may be thrown into the blood-stream and that there is some nice adjustment of mechanism which may have an influence on the further beneficial disposition of these bodies. It is conceivable, however, that at times an undue quantity of such material may overwhelm the regulating mechanism to such a degree that substances which perhaps normally aid in the maintenance of physiological rhythm may indeed become responsible for the advent of abnormal reactions. The suggestion is therefore offered that some of the disturbances associated with excessive intestinal putrefaction may have such an origin. A hypothesis of this sort readily furnishes an explanation for the vaguely

defined headache and general malaise characteristic of the previously mentioned pathological states.

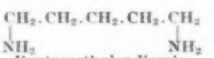
DIAMINES

Cystinuria has been given a great deal of consideration by investigators for the excellent opportunity it afforded of elucidating some of the complex processes underlying the principles of intermediary metabolism. It has been and still is a matter of great uncertainty as to the origin and significance of cystin and the diamins, putrecin and cadaverin, which appear in the excretia of certain individuals. The appearance of cystin has been the subject of such widespread interest, and the results of study of cystinuria have been so extensive and are so well known that further discussion of this subject in this place appears superfluous.[75]

On the other hand, the diamins have not received so much attention. The structure of these bases is as follows:



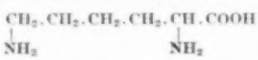
Tetramethylendiamin
Putrecin



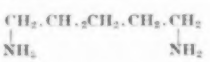
Pentamethylendiamin
Cadaverin

A third diamin, neuridin or saprin, is isomeric with cadaverin. The diamins are eliminated, not only in the urine but also in the feces. As has been stated previously, they are found usually associated with cystin, although the condition responsible for the appearance of cystin in the urine does not seem necessary for the condition of diaminuria, for these substances have also been eliminated under certain other pathological conditions; principally, intestinal disturbances, as for instance, in various infections, in cholera,[83] dysentery, gastro-enteritis,[84] and from one case of pernicious anemia tetramethylendiamin was isolated.[46] The origin of these bodies appears to be in two diamino-acids that are products of normal digestion.

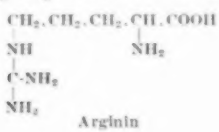
From lysin, which has the following formula:



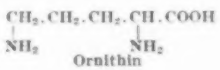
CO_2 is split off, forming cadaverin, with the following formula:



Putrecin is derived ultimately from arginin, guanidin and amino-valerianic acid. Kossel and Dakin[53] have demonstrated the existence of an enzyme, arginase, in certain tissues of the body which is capable of splitting arginin into urea and ornithin. Thus:



Arginin



Ornithin

From ornithin, the formula for which is as follows:

$$\begin{matrix} CH_2.CH_2.CH_2.CH.COOH \\ | \qquad\qquad\quad | \\ NH_2 \qquad\quad NH_2 \end{matrix}$$

CO_2 is split off, forming putrecin, the formula below:

$$\begin{matrix} CH_2.CH_2.CH_2.CH_2 \\ | \qquad\qquad\quad | \\ NH_2 \qquad\quad NH_2 \end{matrix}$$

In intestinal disturbances, it is probable that these compounds are the result of the bacterial activity—indeed they may be the metabolic products eliminated by microorganisms. In cystinuria, however, it is possible that a different[93] explanation for diaminuria is pertinent. It may be assumed, for instance, that in the beginning cystinuria and diaminuria are brought about through a similar, or indeed the same cause, or causes, for example, a gradually changing type of metabolism induced by some unknown agency, resulting in an anomaly of metabolism. If the anomaly is slight in character, cystin alone is eliminated as a result, whereas if the change in metabolism is sufficiently pronounced diamins are also excreted. If this assumption is accepted, it is easy to explain why in some cases of cystinuria the diamins are absent, and that gradually one or both of these compounds disappear, that cystinuria persists, but that cystinuria does not cease and leave diaminuria. Thus far all attempts to produce diaminuria experimentally have been unsuccessful. These bodies are possessed of a certain interest, aside from their chemical significance in that, like nearly all the amins, they are more or less toxic. It has been demonstrated experimentally that the diamins may also exert an influence on certain intermediary processes. Thus, according to Pohl,[81] feeding diamins inhibits certain well-known protective reactions which the organism is capable of putting forth, as for instance, the formation of glycuronates and the synthesis of hippuric acid.

The toxicity of these compounds calls to mind the poisonous action of another diamin, not found in the organism, namely, hydrazin,[94] $\begin{matrix} NH_2 \\ | \\ NH_2 \end{matrix}$ This substance is, however, very much more toxic than the diamins just mentioned. Its introduction into the organism is followed by marked histological changes[99] in various tissues, especially in the liver. In fact, the action of this substance is directed almost specifically on the liver, provoking fatty degeneration of that organ. Only the cytoplasm of the cell is attacked. Although the liver is almost completely transformed under the influence of hydrazin, no noticeable change in nitrogenous intermediary metabolism can be demonstrated through a study of the urinary constituents.

APORRHEGMAS

In a recent communication Ackermann and Kutscher[8] have proposed a new designation for the transformation products of amino-acids which are formed by life processes, whether in the animal or the vegetable kingdom. The term employed for these bodies is "aporrhegma." It is interesting to note the number of such compounds which may arise from putrefaction alone. The above-mentioned authors[8, 9] have given a list of these substances, together with the amino-acids from which they are derived.

AMINO-ACID	APORRHEGMA
Histidin	Iminazolylethylamin
	Iminazolpropionic acid
Arginin	Ornithin
	Tetramethylendiamin
	Aminovalerianic acid
Lysin	Pentamethylendiamin
Glutaminic acid	Aminobutyric acid
Asparaginic acid	Alanin
	Succinic acid
Glycocoll	Methylamin (?)
Leucin	Isoamylamin
	Isovalerianic acid
Prolin	Pyrrolidin
Phenylalanin	Phenylethylamin
	Phenylacetic acid
	Phenylpropionic acid
Tyrosin	Oxyphenylethylamin
	Oxyphenylacetic acid
	Oxyphenylpropionic acid
Tryptophan	Indol
	Skatol
	Indolpropionic acid
	Indolacetic acid

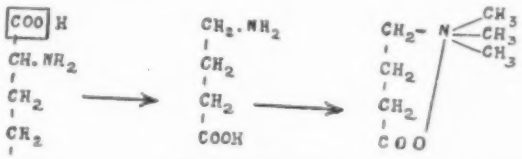
METHYLATION IN THE ORGANISM

Until the last year or two, methylation within the organism was looked on as a reaction which occurred only rarely. With the exception of the well-known examples of the methylation of tellurium[66] and selenium, our knowledge of this type of physiological activity was exceedingly limited. Renewed interest in the process of methylation has been aroused by the recent investigations of Engeland,[37] who has demonstrated that complete methylation of most of the amino-acids derived from the protein molecule is far from a difficult reaction. The betains comprise all that group of bodies of the aliphatic series which are basic in character, thus, such compounds as the various amins, cholin, muscarin, urea, creatin, etc. It is further probable that the wide-spread distribution of the betains, both in the animal and vegetable kingdoms, is to be explained solely by decomposition of protein. Moreover, it has been suggested that all the betains which arise from amino-acids formed by decomposition of protein bear a relation to the so-called "alkaloids."

A methylated amino-acid was unknown in the animal kingdom until completely methylated glycocoll was isolated in considerable quantity from crab meat.[8] Accompanying methyl glycocoll was found trimethylamin oxid.[91]

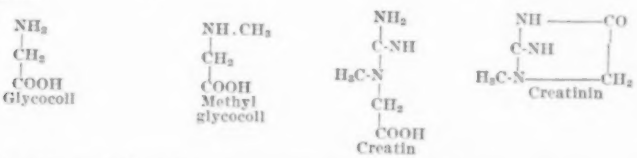
Methyl glycocoll Trimethylamin oxid

Under normal conditions methylation of amino-acids does not occur to any considerable extent in the body of the warm-blooded animals, owing probably to the fact that if such compounds are formed, they are at once oxidized and serve as energy-producing material. When abnormal conditions are induced, however, as in phosphorus poisoning, where, perhaps, oxidative processes are less active the appearance of methylated compounds may be observed. Thus, the methylated gamma amino-butyric acid has been isolated recently from the urine of a dog poisoned with phosphorus.[38] This substance probably arises from glutaminic acid, being transformed into gamma amino-butyric acid, then completely methylated and eliminated.



Glutaminic acid γ amino-butyric acid methylated γ amino-butyric acid

In plants and the lower animals methylated glycocoll is an amino-acid which is very widely distributed. Glycocoll is exceedingly resistant to decomposition by putrefaction, as was long ago demonstrated by Nencki. It is the only amino-acid which appears regularly in the urine, in the form of hippuric acid. It is found in its mono-methylated form as sarcosin combined with the guanidin residue, or modified urea rest, forming creatin of the muscle or creatinin of the urine of the higher animals.



Glycocoll Methyl glycocoll Creatin Creatinin

Creatin and Creatinin.[68, 72]—At present, perhaps the most interesting example of methylation may be found in the origin of the creatin of muscle and the creatinin of the urine. The exact significance of these

compounds is exceedingly obscure. It is known, for example, that under physiological conditions creatin is absent from the urine and that creatinin elimination is practically constant for a given individual. This elimination, however, is different for different individuals, but bears no relation to the volume of the urine or the total nitrogen excreted. From a long series of investigations, it has been concluded that creatinin is an index to some special form of normal metabolism, as yet unknown, but undoubtedly connected with processes concerned with muscle tissue. There is apparently a somewhat close relationship between muscle efficiency and creatinin elimination. Creatinin excretion varies greatly under abnormal conditions, being increased in fevers and diminished in a large number of other pathological states. Particularly striking is the diminution in excretion in abnormal metabolism of muscle tissue and of the liver.

Ordinarily, creatin is absent from the urine, but may be present in large quantities under certain pathological conditions, especially those associated with inanition, depression of liver function, or an abnormal state of muscle. The appearance of creatin in the urine under these circumstances might lead one to infer, by analogy with the presence of the betain of amino-butyric acid noted previously, that when abnormal processes are in order, certain chemical reactions are held in abeyance resulting in the elimination of creatin as an incompletely disintegrated intermediary product. From the most recent investigations[22] concerning creatin and creatinin, it appears likely that there is an intimate relationship between these substances and carbohydrate metabolism, although, at present, this relationship is not more than a mere indication. For example, creatin is present in the urine during fasting both in man and animals. Administration of carbohydrate under these circumstances causes the rapid disappearance of urinary creatin. It has also been suggested that one function of creatin being a base, is to serve as an alkali in the muscle to neutralize lactic acid which arises as a result of muscle activity.[18] Future investigations will, undoubtedly, reveal the significance of the interrelation of creatin, creatinin, muscle and carbohydrate and if the prophecy of Folin, uttered a few years ago before the Harvey society, comes true, the unraveling of this mystery will mean much in the domain of pathology.

THE PROTEOSES

Since the classic experiments of Schmidt-Muhlheim,[59] the behavior of the proteoses when injected into the blood stream has occupied the attention of a long series of investigators, the aim of whom has been to explain the significance of the reactions induced. It had been assumed for years previous to recent times that when proteoses were formed in digestion, they were absorbed into the portal vein, carried to the liver and there were detoxicated. As a matter of fact, it was also discovered

that proteoses introduced into the portal vein were incapable of provoking the typical effects induced by injection into the systemic circulation, an observation in entire accord with the then current views regarding the processes of digestion and absorption.

Renewed activity directed toward the solution of the problem concerning the normal presence of proteoses in the blood was awakened by the more recent investigations having to do with the degradation of the protein molecule in the enteric tract. According to one school, proteoses are absorbed into the blood, thus casting doubt on the prevalent idea that proteoses are broken into their simplest cleavage products, which are absorbed, and then further worked over into the needful compounds. Opposed to this theory is the school that is unable to find any evidence of proteoses in the blood normally. Amid these conflicting views and observations, the apparent consensus of opinion is that proteoses are absent from the blood under normal conditions.[19] Hence, when these substances are introduced into the blood-stream, they act as poisons calling forth certain characteristic reactions, fever, fall of pressure, changes in respiration, increased flow of lymph, saliva, and other secretions, but causing a somewhat prolonged anuria. There has been considerable controversy as to whether *pure* proteoses are really toxic. All the older observations were subjected to severe criticisms by Pick and Spiro,[80] who maintained that proteoses as such are non-toxic and that the toxic principle is merely an adhering contamination, derived from the animal enzymes employed in the preparation of the proteoses. According to these authors, this substance, peptozyme, can be rendered non-toxic by subjecting the proteoses to a certain chemical treatment. Later observations,[96] however, have demonstrated that this conclusion is erroneous, since proteoses prepared from the action of vegetable enzymes on vegetable proteins and also naturally occurring vegetable proteoses induce the same train of symptoms as proteoses made from animal proteins and enzymes. Moreover, cleavage of proteoses beyond the biuret-yielding stage does not produce any symptoms. From the observations of Popielski, it is concluded that the substance responsible for the so-called proteose action may be removed in large measure by treatment with alcohol. This compound has been designated vasodilatin and, according to Popielski,[82] is not protein in nature. The fact, however, that this investigator has not succeeded in separating the vasodilatin from proteoses, together with the well-known fact that a portion of the proteoses are soluble in alcohol, militate against the correctness of the view that the proteoses action is separable from these bodies. On the other hand, it has been suggested[28] that a portion of the reactions provoked by "peptone" may be induced by the presence in the "peptone" of beta iminazolylethylamin which is capable of calling forth symptoms in nearly every respect similar to those produced by the "peptone." The single

exception noted is that beta iminazolylethylamin does not render the blood non-coagulable, which is distinctly characteristic for "peptone."

In our laboratory the observation has been made recently that the intravenous injection of proteoses produces a significant glycosuria. Coincident with the appearance of sugar in the urine, there is a marked hyperglycemia. The cause and possible significance of this reaction is being investigated. It appears a little strange that, of the long series of investigations carried out with the proteose injections, in not a single instance is there a recorded observation indicating glycosuria. When proteoses are injected into the blood-stream, the major portion of these compounds promptly reappears in the urine, although there is some evidence that they may be partially transformed into smaller molecules.[28] Albumosuria, so-called, is indicative of the formation of proteoses within the organism and is considered of importance in diagnosis. Thus, albumosuria may be observed in suppuration of all kinds, resolution of pneumonia, involution of the uterus, carcinoma, atrophy, eclampsia, leukemia, absorption of simple and inflammatory exudates, febrile conditions with destruction of tissue, and ulcerating pulmonary tuberculosis.[100]

It is possible, and indeed may be probable, that the proteoses formed within the body and thrown into the blood-stream may be responsible for some of the symptoms which are characteristic of some of the abnormal conditions cited. The fact that these substances are fairly toxic is almost evidence for the possibility just indicated. The significance of these compounds, both in physiology and pathology, warrants further investigation of the cause of the symptoms induced. It is hardly probable that any one specific group in these complex polypeptids is responsible for all the reactions noted and future study will undoubtedly demonstrate the presence of several distinct entities which specifically call forth certain symptoms.

The modern conception of the living cell makes enzymes responsible for the numerous types of known activities; thus we speak of enzymes facilitating reduction, oxidation, deamination, cleavage, etc. One organ is found to contain enzymes active to a high degree in one direction, another organ in another direction, and still a third organ which may furnish an almost unlimited number of enzymes capable of performing varied types of reactions. Ordinarily when enzymes are mentioned, one thinks involuntarily of the best-known agents, the digestive ferments. Our ideas concerning the exact mode of action of the enzymes that undoubtedly play an important rôle in intermediary metabolism are not well defined. It is probably, however, not an unwarranted position to assume that the several types of reactions discussed in previous portions of this paper have enzyme activity as their basis.

With the acceptance of enzyme activity as the foundation of cellular chemical activity, hence, intermediary processes, it is easy to conceive

how the induction of abnormal environment for these agents may lead to the production of distinctly pathological phases of metabolism with consequent injury to the whole physiological economy. In our endeavor to discover the reason, or the cause, for abnormal metabolism we have been led into the error of looking for changes of too great magnitude. Enzymes are exceedingly sensitive to all sorts of changes in environmental conditions. Too much acid, or too little, lack of the requisite inorganic salts, perhaps absence of carbohydrate—that group of substances vaguely designated as co-enzymes—may retard or hold in abeyance certain types of reaction the effects of which, over a considerable period of time, work injury to other types of enzymes until finally a large number of processes may be carried out only imperfectly.[105] Perhaps one of the best examples of the point under discussion may be taken from the recent work of Bywaters,[20] who found that the inverting power of an aqueous extract of yeast is increased ten- to fifteen-fold by the addition of acetic acid. On the other hand, this activity given by acid addition is susceptible of removal by alkalies, which subsequent addition of acid is capable of counteracting. Under one form of environment the power disappears and when changed to another the power is restored.

With data of this type at hand, is one unwarranted in suggesting the probability that pathological metabolism of various types may be the direct result of changed environmental conditions of intracellular enzymes? I believe that such a viewpoint will do much toward a solution of many problems concerning metabolism both from the standpoint of physiology and pathology, the dividing line of which is exceedingly narrow.

The advances of the future are to be made, I believe, by a careful study of small changes, details which at first thought perhaps appear insignificant but if followed will lead to far-reaching results. One of the best examples that can be cited in this connection may be taken from a recent paper on "The Influence of Alcohol on Nitrogenous Metabolism" by Mendel and Hilditch.[69] As a result of their study, the authors conclude that "the most significant impression, perhaps, which the analytical data afford, is the absence of *pronounced* alterations indicative of markedly disturbed protein metabolism." Emphasis on the words "absence of *pronounced* alteration" shows an entire appreciation of the presence of small differences. In this particular case, the organism was capable of using certain doses of alcohol to its distinct advantage; beyond this limit changes in purin output were observed. The cellular mechanism was altered in such a manner that certain types of processes were changed in a measure, the extent of the change being indicated by the altered purin output. The changed output was not large, but was it not just as good an indication of deranged metabolism as if the change had been twice as great? If the view suggested is correct, then the hope of future advances along the line of intermediary metabolism lies in an

appreciation of the significance of small differences and changes in the environmental conditions of the cell.

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STUDIES ON WATER-DRINKING

VI. THE ACTIVITY OF THE PANCREATIC FUNCTION UNDER THE INFLUENCE OF COPIOUS AND MODERATE WATER-DRINKING WITH MEALS *[1]

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Numerous tests are in vogue clinically for the determination of the functional activity of the pancreas. The best known of these are the glutoid test of Sahli,[2] the nuclei test of Schmidt,[3] and the Cammidge[4] reaction, the last mentioned test having been rather more freely criticized than either of the others. Comparatively recently, clinicians have come to a fuller realization of the aid which a knowledge of the pancreatic enzyme concentration of the feces may give them in their diagnosis of pancreatic insufficiency. The accurate determination of the enzyme content of the feces under normal or pathological conditions is still, however, a line of medical research which has not been very generally investigated. Some of the investigators who have recently contributed to our knowledge in this direction either by suggestions as to method or by the collection of clinical data are Müller,[5] Wohlgemuth,[6] Wynhausen,[7] Boldyreff,[8] Abderhalden and Schittenhelm,[9] Schlecht,[10] Goldschmidt,[11] Volhard,[12] Ury,[13] Frank and Schittenhelm.[14] One of the first enzymes to be

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1. For previous papers in this series of studies see, I. Hawk: Univ. Penn. Med. Bull., 1905, xviii, 7; II. Fowler and Hawk: Jour. Exper. Med., 1910, xii, 388; III. Rulon and Hawk: Jour. Am. Chem. Soc., 1910, xxxii, 1686; IV. Rulon and Hawk: THE ARCHIVES INT. MED., 1911, vii, 536; V. Hattrem and Hawk: THE ARCHIVES INT. MED. 1911, vii, 610.

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detected in the feces was pancreatic amylase. This enzyme, as early as 1875, was shown by Wegscheider[15] to be present in the feces of the nursling. This finding was later verified by von Jaksch,[16] Moro[17] and Allaria.[18] According to this last-mentioned investigator the manner of feeding the infant, i. e., naturally or artificially, had no influence on the amylase concentration of the feces. Strasburger[19] found this same condition to hold for the stools of adults.

DESCRIPTION OF EXPERIMENTS

Three experiments were made, in each of which normal men (E and W) served as subjects, the same man serving as subject in Experiments 2 and 3. Each experiment was divided into three periods, a *fore* period during which the subject was brought into nitrogen equilibrium through the ingestion of a diet uniform as to quality and quantity from day to day, a *water* period during which the ration was supplemented by the drinking of additional water at meal-time, and finally an *after* period in which the *fore* period ration of low water content was again fed. The constituents of the diet apart from the water were graham crackers, butter, milk and peanut butter. The diet of Subject W in Experiment 1 contained 85.8 gm. of protein per day whereas that of Subject E in Experiments 2 and 3 contained 92.3 gm. of protein per day. During the *fore* and *after* periods of each experiment 100 c.c. of water, in addition to the water content of the milk, was taken by each subject at each meal. In the *water* periods of Experiments 1 and 2, 500 c.c. of water above that previously ingested were taken with each meal, whereas in Experiment 3 this volume was increased to 1⅓ liters.

Each individual stool was examined in the fresh condition. The feces of one period were separated from those of the next by means of charcoal, the material being ingested in gelatin capsules at the beginning of the first meal of each new period.

The method used in the quantitative determination of the activity of the pancreatic function was that suggested by Wohlgemuth.[8] This author considers that the extent to which pancreatic amylase appears in the feces may be taken as an index of the activity of the pancreatic function. He therefore suggests a procedure for the quantitative determination of the amylolytic power of sodium chlorid extracts of the fresh feces. His procedure has been fully discussed by us in another connection and a modification of the Wohlgemuth method proposed.[20] In the experiments

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embraced in the present paper, however, the procedure used by us was essentially that of Wohlgemuth except that the final amylolytic values of the stools were calculated in terms of dry matter instead of on the basis of the moist sediment secured by centrifugation as Wohlgemuth suggests.

In order to demonstrate conclusively the origin of the fecal amylase Wohlgemuth[6] has made certain interesting tests. In these tests it was demonstrated that the ligation of the pancreatic ducts of dogs caused the feces as passed to be amylase-free or to contain at the most a minimal quantity of the enzyme. Wynhausen[21] has likewise found a much-decreased amylase output in cases with partial closure of the pancreatic duct.

TABLE 1.—FECAL AMYLASE, EXPERIMENT 1, SUBJECT W, MODERATE WATER-DRINKING

	Feces		Amylolytic Value—1% Starch	
Stool No.	Fresh (grams)	Dry (grams)	Total (liters)	Per Gram Dry Matter (c.c.)
FORE PERIOD—SIX DAYS				
1	62.8	16.1	11.4	709
2	98.8	26.4	10.8	409
3	109.8	30.2	18.1	600
4	185.8	44.8	26.3	587
5	41.8	13.1	6.7	513
6	104.9	25.5	20.9	819
7	24.6	7.9	3.3	416
Average per day.....	104.6	27.3	16.3	597
WATER PERIOD—TEN DAYS (1,500 c.c. H_2O daily)				
8	31.6	7.6	7.6	1,000
9	147.5	40.6	34.9	860
10	75.4	19.8	17.1	865
11	144.8	39.8	27.3	688
12	63.9	17.2	14.6	848
13	115.5	31.3	22.2	709
14	26.0	7.2	4.0	548
15	169.0	44.8	32.5	725
16	127.0	30.9	44.7	1,447
17	152.7	35.5	110.3	3,106
Average per day.....	105.3	27.5	31.5	1,145
AFTER PERIOD				
18	60.0	14.8	14.6	983
19	119.6	28.0	39.4	1,052
20	51.1	14.1	20.8	1,477
21	142.7	35.8	41.1	1,147
22	81.4	22.8	15.0	657
23	53.4	16.4	19.1	1,162
Average per day.....	101.6	26.3	28.0	1,065

DISCUSSION OF RESULTS

1. Moderate Water-Drinking.—Data from the first experiment may be found in Table 1. The subject of this experiment was W and the purpose was the study of the influence of moderate water-drinking *with meals* on the activity of the pancreatic function. After a fore period of six days on a uniform diet, as already mentioned, the subject was found to be in nitrogen equilibrium as was shown by a nitrogen balance of 0.01 + gm. The average daily output of fresh feces was 104.6 gm., representing a dry matter content of 27.3 gm. per day during this period.[22] The total

21. Wynhausen: Berl. klin. Wchnschr., 1909, No. 30.

22. The data for fresh and dry feces were obtained by Dr. H. A. Mattill in connection with another research which has already been reported. See Mattill and Hawk: Proc. Soc. Biol. Chem., 1911.

amylolytic value of the stools per day, expressed in liters of 1 per cent. starch solution which this feces would hydrolyze under the conditions of the Wohlgemuth method, was 16.3 liters. Placed on the basis of "1 gm. of dry feces" we see by an examination of the data that the average daily amylolytic value for this period was represented by 597 c.c. of 1 per cent. starch solution.

Under the influence of the 500 c.c. of water ingested at each meal for a period of ten days there was a marked increase in the amylolytic power of the feces. For example, the data from the first stool of this period indicate that the amylolytic value was 1,000 c.c. of 1 per cent. starch solution per gram of dry feces. This initial value of the period was far above that for any individual stool of the fore period and nearly double that of the daily average amylolytic value (597 c.c.) for the entire fore period. If the data from the analysis of the stools which were subsequently dropped during this *water* period are examined it will be seen that the amylolytic values for these stools, with a single exception (No. 14), were above the average value for the fore period. It will furthermore be observed that the average amylolytic value for the water period, i. e., 1,145, was approximately twice as great as the average amylolytic value for the fore period. In other words the drinking of 1,500 c.c. of water per day, at meal time, through a period of ten days, was instrumental in causing a virtual doubling of the amylolytic activity of the fecal matter excreted during that period as compared with the fecal output of the fore period during which minimal amounts of water were daily ingested.

The significance of this finding of an increased amylolytic power is further accentuated when the data from the after period are examined. Notwithstanding the fact that the water ingestion of this period was reduced to the low level of the fore period the stools as dropped were on a much higher amylolytic plane than were those of the fore period. This fact is clearly brought out when it is noted that the corresponding values for the fore and after periods were 597 and 1,065 respectively. We thus see that the stimulation of the factors which brought about the increased amylolytic power of the fecal output of the water period was not transitory in character. In other words the influence of the water was not limited to the time of its ingestion, but the factors leading to an increased fecal amylolytic value were so stimulated by the ingestion of the excess water as to continue their efficiency even after the water ration had been again reduced to that of the fore period. Whether this pronounced increase in amylolytic power observed to accompany and follow the ingestion of additional volumes of water at meal time may be properly interpreted as indicative of an increased activity of the pancreatic function is discussed in a later paragraph.

In the second experiment on the influence of moderate water drinking (Experiment 2) E served as subject. All conditions were the same as those in force in the similar experiment on W with the exception that the uniform diet was varied in a minor manner from that ingested by W. The data obtained from the fecal examinations of this experiment are tabulated in Table 2. In this instance approximate nitrogen equilibrium was secured in seven days, the nitrogen balance showing a plus value of 0.485 gm. per day. A ten-day water period then followed during which 500 c.c. of water were ingested with each meal in addition to the uniform water ingestion of the fore period. The experiment ended with a four-day after period.

TABLE 2.—FECAL AMYLASE, EXPERIMENT 2, SUBJECT E, MODERATE WATER-DRINKING

	Feces		Amylolytic Value—1% Starch	
Stool No.	Fresh (grams)	Dry (grams)	Total (liters)	Per Gram Dry Matter (c.c.)
FORE PERIOD—SEVEN DAYS				
1	88.4	18.4	6.3	343
2	30.2	8.0	3.9	491
3	179.2	41.2	14.0	341
4	193.9	47.8	11.3	237
5	76.9	20.1	3.7	184
6	207.7	47.3	16.3	345
7	124.6	27.8	15.3	548
8	44.0	12.9	2.2	171
Average per day.....	135.0	32.0	10.4	325
WATER PERIOD—TEN DAYS (1,500 c.c. H_2O daily)				
9	76.5	17.5	7.3	418
10	140.9	29.4	31.6	1,075
11	63.8	18.6	2.3	124
12	169.0	41.1	16.1	393
13	247.5	47.5	12.1	255
14	135.3	31.1	6.2	198
15	192.4	37.7	19.7	522
16	79.2	19.5	15.6	801
17	55.9	15.2	9.3	613
18	173.5	43.2	27.5	636
19	51.5	14.4	9.2	642
Average per day.....	138.6	31.5	15.7	498
AFTER PERIOD—FOUR DAYS				
20	67.3	15.9	14.0	878
21	117.8	30.7	19.9	649
22	147.7	34.3	21.8	637
23	145.9	38.7	25.8	667
24	31.2	9.8	9.4	961
Average per day.....	127.5	32.3	22.7	703

During the preliminary interval of low water ingestion covered by the fore period the average daily total amylolytic value of the feces was equivalent to 10.4 liters of 1 per cent. starch solution. Placed on a *dry-matter basis* we find that the amylolytic value of the feces of this period may be represented by 325 c.c. of 1 per cent. starch solution per gram of dry matter. If we now examine the data for the period during which the extra volume of water was ingested we find that the conditions are similar to those already discussed in connection with the experiment in which W served as subject. In other words, water caused an increase in the amylolytic value of the feces. The average total daily amylolytic

value for the water period was 15.7 as against 10.4 for the fore period whereas the value on the dry matter basis was 498 as compared with a value of 325 for the preliminary interval.

The influence of the moderate water-drinking in causing an increase in the amylolytic power of the feces was much less pronounced with E than with W. This statement is borne out by the observation that there was an increase of nearly 100 per cent. in the case of W as against an increase of little more than 50 per cent. in the case of E. However, when we examine the data for the after periods of the two experiments in question, we note that the amylolytic value in E's experiment was above that of the water period, whereas in W's experiment this value was slightly lower than that of the water period. By calculation we see that the amylolytic value for the after period of the test on W was increased only 80 per cent. above that of the fore period whereas the increase in the test on E was about 120 per cent. It would seem, therefore, that the water caused a more pronounced immediate stimulation in the case of W than in that of E but that the influence of the stimulation was more persistent in the case of E than in that of W.

TABLE 3.—FECAL AMYLASE, EXPERIMENT 3, SUBJECT E, COPIOUS WATER-DRINKING

Stool No.	Feces: Fresh (grams)	Feces: Dry (grams)	Amylolytic Value—1% Starch: Total (liters)	Amylolytic Value—1% Starch: Per Gram Dry Matter (c.c.)
FORE PERIOD—SIX DAYS				
1	35.2	10.2	3.8	375
2	66.0	18.8	8.6	458
3	202.2	49.8	23.6	473
4	129.2	32.2	14.9	464
5	161.3	34.6	8.8	256
6	171.8	38.8	15.8	406
7	34.6	9.4	4.2	448
Average per day.....	133.4	32.3	13.3	412
WATER PERIOD—FIVE DAYS (4,000 c.c. H_2O daily)				
8	90.3	18.2	10.5	578
9	37.2	10.2	8.3	816
10	249.4	58.8	26.5	451
11	74.7	19.9	6.1	306
12	258.0	38.2	342.3	8,961
13	52.6	15.9	7.8	491
Average per day.....	152.5	32.2	80.3	2,494
AFTER PERIOD—THREE DAYS				
14	128.3	29.6	12.3	414
15	86.4	21.0	15.6	743
16	206.5	44.5	25.0	561
17	50.6	5.6	7.0	1,257
Average per day.....	157.3	33.6	20.0	595

2. Copious Water-Drinking.—The amylolytic power of the feces was studied in but one experiment in which copious water drinking was practiced at meal time. In this experiment (3) E served as subject. All the experimental conditions were similar to those in force with this same subject in the second experiment on moderate water drinking. In a fore period covering an interval of six days a very satisfactory balance for income and outgo of nitrogen was obtained, the data indicating a plus balance of only 0.03 gm. The data from this experiment are given in Table 3. An examination of that table will show, in the first place, that

the average total daily amylolytic value for the fore period was 13.3, whereas the amylolytic value on a dry matter basis was 412. These values simply mean, as heretofore explained, that the average output of feces per day during the six-day fore period possessed the power to hydrolyze 13.3 liters of 1 per cent. starch solution, whereas 1 gm. of dry feces possessed the power of transforming 412 c.c. of such a starch solution.

The water period of this experiment was five days in duration as against the ten-day periods utilized in the experiments already discussed. However, the daily ingestion of water was much higher in this instance than in either of the afore mentioned studies. In the *moderate* water-drinking tests we caused the subjects to ingest 500 c.c. additional at each meal or a total daily ingestion of 1,500 c.c. in excess of that customarily taken. In certain other water-drinking studies made by us (Fowler and Hawk[1]; Mattill and Hawk[22]; also Wills and Hawk, unpublished), in which the influence of *copious* amounts of water was under investigation, the total volume of water added daily to the normal ration had been 3,000 c.c. However, in the present investigation we were dealing with a subject, E, who was accustomed to drinking rather larger volumes of water than individuals ordinarily ingest and for this reason his water ration was fixed at 4,000 c.c. per day during the water period in an attempt to place the daily volume at such a figure as should be copious for his organism. He felt no personal discomfort at any time during the period in which this excessive amount of water was being daily introduced into his system.

Under the influence of copious water-drinking through a five-day period, the amylolytic activity of E's feces was increased in an extremely emphatic manner. Particularly was this true of Stool 12, passed on the fourth day of the period. Expressing the amylolytic values in the same manner as heretofore followed we find that the average amylolytic power of the feces was equivalent to a force sufficient to hydrolyze 80.3 liters of 1 per cent. starch solution. Furthermore, if we transfer the comparison to the dry-matter basis we learn that 1 gram of dry matter represents sufficient amylolytic activity to hydrolyze 2,494 c.c. of 1 per cent. starch solution. When we compare these volumes with those obtained during the fore period we are astounded at the very material increase in the amylolytic activity which has taken place under the influence of the copious water-drinking. For example, if we consider the dry-matter basis we see that the amylolytic value has increased from 412 to 2,494, a most surprising increase of more than 600 per cent. in the amylolytic activity. The question as to the proper interpretation of this finding, in so far as it relates to the functional activity of the pancreas, is discussed later on. In this experiment for the first time, we observed an amylolytic value for the after period which was lower than that of the water period. Evi-

dently the stimulation of the copious water-drinking was so pronounced in character in this particular instance as to rather militate against any further added stimulation after the organism was released from the immediate influence of the water ingestion. That the influence of the water extended somewhat beyond the time interval during which it was actually being ingested is gathered from the recorded average amylolytic values for the after period. These values are nearly 45 per cent. above those of the fore period thus indicating an after effect which persisted for a time, at least, after the period of high water intake had closed.

INTERPRETATION OF FINDINGS

The foregoing discussion of the various experiments embraced in this study has indicated clearly that when either small or large volumes of water above those customarily ingested were taken at meal time that the resultant fecal matter possessed greater amylolytic activity than did the feces passed during periods in which these extra volumes of water were not taken. How is this finding to be interpreted? It has been established that an increase in the activity of the pancreatic function will be indicated by the appearance of an added excretion of pancreatic amylase in the feces. This fact would of itself cause the feces in question to possess an increased power to hydrolyse starch solution. On such a basis Wohlgemuth has suggested a method for the quantitative determination of the amylolytic power of the feces. This power, according to Wohlgemuth, is due entirely to the ability of dilute solutions of the fecal amylase to transform starch into substances which no longer give a blue color with iodin. From this point of view, therefore, we may interpret our results as indicating that the pancreatic function has been greatly stimulated under the influence of the water-drinking at meal-time and that consequently larger quantities of pancreatic amylase are present in the feces passed during the water period, thus giving to the fecal matter a higher amylolytic power than that possessed by stools dropped during previous periods in which the water ingestion was minimal.

We began our investigation under the impression that Wohlgemuth's method would furnish us with accurate data, and nothing occurred in the course of the experiments to cast any doubt on the validity of Wohlgemuth's claim until an examination was made of the final stool (17) in the water period of Experiment 1. Here for the first time in the course of our studies the entire series of seven tubes of 1 per cent. starch solution showed complete digestion. As soon as this fact was determined another series of ten tubes was prepared and again the entire series was completely digested. Not caring to rely on data obtained from further extracts because of the possibility of changes having taken place in the feces, we examined no further series. A similar observation was made in

connection with Stool 12 in Experiment 3. In our search as to the cause of this surprisingly pronounced increase in the amylolytic activity of the stools mentioned, we observed that they each possessed a very pronounced acid reaction. We were familiar with the findings of Chittenden and Griswold,[23] which were later confirmed by Vernon[24] to the effect that amylase (salivary) is inactive in the presence of 0.009 per cent. hydrochloric acid. At the same time we were familiar with the further fact that it requires an acid concentration much above 0.009 per cent. hydrochloric acid to hydrolyze 1 per cent. starch solutions under the conditions of our experiment. Furthermore, in the experiments of Vernon to which reference has already been made, as well as in others by Schierbeck,[25] it has been demonstrated that certain proper acid concentrations below 0.009 per cent. hydrochloric acid will facilitate the activity of amylase. This power was shown to be possessed by organic acids as well as by inorganic acids. In the case of hydrochloric acid a concentration of 0.004 per cent. was found to cause an increase of 400 per cent. in the amylolytic power of the enzyme, whereas 0.0083 per cent. lactic acid increased the amylolysis nearly 500 per cent.

In light of the above findings, we might interpret the fivefold increase in the amylolytic power of acid Stool 17 of Experiment 1 and the sixfold increase in the amylolytic power of acid Stool 12 of Experiment 3 as due to the stimulating influence of the acid reaction of the sodium chlorid extracts of the feces on the contained amylase. It obviously needs no argument to support the claim that the acidity of these extracts could not of itself have caused the hydrolysis of the 1 per cent. starch solutions. Even had the feces possessed a surprisingly high acid concentration, this concentration must of necessity have been so much lowered by the time the series of dilutions of the salt solution extracts had been made as to render the acidities, of the latter part of the series, at least, of no influence in so far as their power to hydrolyze starch is concerned. It is entirely possible that the amylase was passed into the intestine in increased amount on the days in question under the influence of the high water intake, that it there fulfilled its function of bringing about an augmented amylolysis and that subsequently the reaction of the surrounding media was so altered by certain factors as to render impossible any further activity of the enzyme. Therefore the reaction in which the enzyme was finally excreted from the organism by way of the feces was not, of necessity, the reaction which the intestinal substrate of the pancreatic amylase possessed. Be that as it may, however, it is of course impossible to come to any definite conclusion as to the extent of the stimulation of the activity of the pancreatic function on the basis of data collected from acid

23. Chittenden and Griswold: Am. Chem. Jour., 1881, iii, 305.
24. Vernon: Jour. Physiol., 1902, xxvii, 174.
25. Schierbeck: Skand. Arch. f. Physiol., 1892, iii, 344.

stools by means of the Wohlgemuth method. This being so, we have suggested a modification of that method which should obviate the troublesome features associated with the examination of stools which possess a pronounced acid or alkaline reaction. This method appears elsewhere.[26]

If we examine the data in Tables 1, 2 and 3 it will be seen that the complete elimination of all consideration of the acid stools in question which gave evidence of the surprisingly pronounced amylolytic power, will not prevent us from drawing the conclusion that the activity of the pancreatic function was stimulated under the influence of water-drinking at meal time. Certain other experiments may be cited as tending to substantiate the theory of an increased activity of the pancreatic function under the influence of water-drinking with meals. For example, Pawlow[26] has shown that if 150 c.c. of water be introduced into the stomach of a dog possessing a pancreatic fistula, that the flow of juice begins after an interval of two or three minutes and in case there is already present a distinct flow of juice that the output is distinctly increased. That this flow of juice was not brought about through the stimulation of acid chyme entering the duodenum was shown from the fact that, if the stomach of the animal be emptied, the contents of the organ are found to be neutral or faintly alkaline in reaction. This experiment by Pawlow indicates clearly, then, that water introduced into the stomach causes a direct stimulation of the nervous mechanism of the pancreas which is followed by an outpouring of pancreatic juice. As further basis for our belief that water ingestion stimulates the pancreas, we would cite certain other experiments of Pawlow[27] and the earlier work of Heidenhain[28] and Ssanozki.[28] The more recent experiments of Foster and Lambert[29] may also be adduced as furthering this claim. These various investigators just enumerated have shown that an increased flow of gastric juice follows the entrance of water into the stomach. The studies of Foster and Lambert go even farther than this and show most clearly that there is not only an increased flow of juice but that this increased volume possesses a higher acid concentration than that possessed by juice secreted under other conditions. We have obtained results in this laboratory[30] which go to verify the findings of Foster and Lambert. On the basis of the well-established theory as to the mechanism of pancreatic secretion as evolved by Bayliss and Starling[31] we may logically expect a pronounced increase in the flow of pancreatic juice to follow the entrance of the strongly acid chyme into the duodenum. That the pancreas is more active under a

26. Pawlow: The Work of the Digestive Glands, Second Edition, 1910, p. 144.
27. Pawlow: The Work of the Digestive Glands, p. 112.
28. Quoted by Pawlow, p. 112.
29. Foster and Lambert: Jour. Exper. Med., 1908, x, 820.
30. Wills and Hawk: Proc. Soc. of Biol. Chem., 1911.
31. Bayliss and Starling: Jour. Physiol., 1902, 28.

high water ingestion is also evidenced from other experiments made in this laboratory[22] which have demonstrated a more complete digestion and absorption of ingested fats and carbohydrates under the influence of water-drinking at meal time.

It has further been found by us[32] that the carbohydrate content of the actual samples of feces listed in Tables 1, 2 and 3 of this article was lower during the water periods than during the period of minimal water ingestion. This fact demonstrated definitely then that the intestinal content of these subjects was of a higher amylase concentration during the period of increased water intake. Other things being equal we would expect a fair degree of uniformity between the availability of ingested carbohydrate and the content of fecal amylase. The observation of Bradley[33] to the effect that pancreatic lipase possesses greater fat-splitting power when its reaction mixtures are diluted with several volumes of water also goes far toward a substantiation of the theory of a pancreas activated through water ingestion.

We have much to learn as to the alterations in the reaction of the intestine under different conditions. In the case in point we have an excessive quantity of hydrochloric acid passed into the intestine, under the influence of the high water intake, a quantity which probably, at times, is far in excess of that which may be neutralized by the pancreatic juice and bile. The greater portion of this excess acid we may suppose to be neutralized by the ammonia which is produced in the deamidation of protein material. This acid would therefore appear in the urine as ammonium chlorid. However, if there should occur a very copious outpouring of hydrochloric acid at a time when there was but little protein material available for deamidation and consequently a minimal amount of ammonia present for the neutralization of such excess acid, it is entirely possible that we might have an acid reaction due to hydrochloric acid extending the entire length of the large intestine. In that event the stools would probably possess a relatively high acid concentration. If the food residues remained in the intestine for an interval shorter than the normal because of increased peristalsis, diarrhea, etc., acid stools might also result.

The normal reaction of the intestinal contents is acid down to the ileocecal valve under normal conditions. Furthermore, carbohydrates which escape absorption may undergo acid fermentation through the action of certain acid-forming bacteria such, for example, as *Bacillus coli* and *Bacterium welchii*. A number of organic acids are formed which include acetic acid, lactic acid, butyric acid and succinic acid. The extent to which this acid reaction may be carried is indicated by Macfadyen,

32. Mattill and Hawk: Unpublished results.
33. Bradley: Journal Biol. Chem., 1910, viii, 251.

Nencki and Sieber's[34] finding of an acidity at the ileocecal valve equivalent to 0.1 per cent. acetic acid. This observation was made on a patient with a fistula at the end of the small intestine.

SUMMARY

The problem studied was the activity of the pancreatic function under the influence of water-drinking at meal time. Normal men were used as subjects and were required to ingest a diet uniform in all respects from day to day. Three experiments were made, each experiment being divided into three periods; a *fore* period in which the subject was brought into nitrogen equilibrium through the ingestion of the uniform diet supplemented by a minimal water ingestion; a *water* period during which the water ingestion at meal time was increased from 1,500 to 4,000 c.c. per day; and an *after* period in which the dietary conditions of the fore period prevailed. Two of the experiments were on the influence of *moderate* water-drinking and in these the volume of the extra water ingested during the water period was 1,500 c.c. per day or 500 c.c. per meal. In the third experiment the influence of *copious* water-drinking was studied and in this instance the subject was required to ingest on each day of the water period 4,000 c.c. above that ingested in the fore and after periods.

The amylolytic activity of the feces, denoting, according to Wohlgemuth, the content of pancreatic amylase present in the feces, was taken as the index of the activity of the pancreatic function. The amylolytic values for the stools dropped during the periods of moderate and copious water-drinking at meal-time were much higher than the similar values as determined for the stools dropped during the periods of minimal water ingestion. This finding may be interpreted as indicating that the drinking of water with meals had stimulated the pancreas. We make this interpretation with certain reservations regarding conditions not controlled by the Wohlgemuth method. Two stools were encountered in the course of the investigation which exhibited a pronounced acid reaction. Inasmuch as the basic principle of Wohlgemuth's method is the hydrolysis of starch solutions through the medium of unneutralized fecal extracts, the method does not give dependable data as to the amylase content when such stools are under examination. This is true especially in view of the fact that it has been shown that 0.004 per cent. hydrochloric acid will increase the activity of amylase 400 per cent., whereas 0.009 per cent. hydrochloric acid will cause absolute inhibition. The power of feces extracts, therefore, to hydrolyze starch cannot be taken as a measure of the amylase present unless precautions are taken to neutralize the fecal extracts and then make the conditions uniform for the action of the enzyme if present.

34. Macfadyen, Nencki and Sieber: Arch. f. exper. Pathol. u. Pharmacol., 1891, xxviii, 311.

On the basis of the data gathered in this and in associated investigations made in our laboratory and elsewhere, we are prepared to draw the general conclusion that the ingestion of quantities of water at meal-time ranging in volume from ½ to 1⅓ liter stimulate the pancreatic function in two ways: first, a direct stimulation of the nervous mechanism of the pancreas brought about while the water is still in the stomach and, second, an indirect stimulation brought about on the entrance of the increased volume of acid chyme into the duodenum. The drinking of water with meals ought therefore to bring about a more rapid and complete digestion and absorption of the fat and carbohydrate constituents of the diet, two observations verified by experimentation in our laboratory.

THE IMMEDIATE EFFECT ON THE COMPLEMENT FIXATION TEST FOR LUES OF TREATMENT WITH SALVARSAN (ARSENOBENZOL)

AN ANALYSIS OF 225 CASES*

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In reviewing the literature on the results of the treatment of lues with salvarsan, one is impressed with the unsatisfactory nature of the data regarding the effect of treatment with this drug on the complement fixation test. It is now generally acknowledged that this test is the only exact index we possess of the efficacy of any method of treatment of lues; indeed, Ehrlich[1] does not hesitate to say that "the observation of the Wassermann reaction represents the most valuable method we have of seeing clearly whether the syphilis is genuinely cured," and this opinion is supported by every authority having to do with the treatment of the disease.

In view of the importance of the complement fixation test as a control of the efficacy of treatment with salvarsan, I have thought that an analysis of 225 cases, showing the immediate effect of such treatment on the test, would be of interest and value. I have used the term "immediate effect" because it is yet too early to speak of the ultimate effect of this method of treatment on the complement fixation test. It is believed that the data obtained from the cases reported on are especially valuable, because in the vast majority numerous tests have been made at frequent intervals, thus giving one a more just conception of the exact effect of treatment with this drug on the complement fixation test. It will be observed that an early disappearance of a positive reaction is more frequently noted in this series of cases than is reported by most observers, largely owing to the fact that the tests were made at frequent intervals, a practice possible only in the military service or where luetic patients can be kept under constant observation for long periods of time. In the military service, also, it is possible to secure more accurate data regarding the date of infection and the nature and extent of previous treatment.

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*Published with the authority of the Surgeon General, U. S. Army.

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1. Ehrlich, P.: Chemotherapy, Ed. 1, New York, 1911, p. 116.

facts of great importance in any consideration of the effect of treatment with salvarsan on the complement fixation test.

Before considering the results obtained in this laboratory, it is necessary briefly to discuss the exact clinical significance of the positive and negative reaction after treatment with salvarsan. I believe that it may be stated without hesitation that a positive Wassermann reaction means the presence of living spirochetes and is always an indication for further treatment, provided a sufficient time has elapsed for the reaction to become negative, as shown by experience. On the other hand a negative reaction does not necessarily mean that all the spirochetes are destroyed, for relapses may occur after the reaction has been negative for weeks or even months. A negative reaction may, therefore, mean either a complete cure or only the destruction of a sufficient number of the spirochetes to prevent the appearance of the reaction. The latter statement is supported by the occurrence of cases in which the patients are suffering from a clinical relapse, but in which the complement fixation test remains negative for some time. In one such case the spirochetes were demonstrated in the lesions at the time of the relapse, although the reaction was still negative, thus proving that the mere presence of the parasites is not always accompanied by a positive Wassermann test. Well-marked clinical cases of lues are also observed, in which the Wassermann test is negative, although the lesions contain the spirochetes and no treatment has been administered. It would, therefore, appear as though the appearance of a positive reaction depends on quantitative phenomena or on reactions of the tissues to the spirochetes which may not occur under certain conditions.

As I have stated the literature regarding the effect of treatment with salvarsan on the complement fixation test is limited in amount, and much of it is unsatisfactory in character. While many authorities have reported very fully the clinical results in thousands of patients so treated the serologic data are generally incomplete, many of the most valuable clinical reports containing either no mention of the results of the complement fixation test or recording them inaccurately or in such a way that no definite conclusions can be drawn from them. A few writers, however, have reported in detail the results of the Wassermann test in their cases but it is difficult to judge of their value, as a whole, on account of the lack of data regarding many important factors having to do with the time of disappearance of the reaction. A brief abstract is given of the most important contributions to this subject.

Nichols and Fordyce[2] report the results of the Wassermann test in eleven patients treated with salvarsan. In eight the reaction became negative, one in nineteen days; two in twenty-one days; one in twenty-three days; one in twenty-five days; one in thirty-nine days; one in three months; and one in three months

2. Nichols, H. J., and Fordyce, J. A.: Jour. Am. Med. Assn., 1910, lv, 1171.

and eleven days. Of these cases, two are still negative at the end of ten months, a period of time sufficient, I believe, to prove that they are cured. In both of these cases, the dose of arsenobenzol was only 0.3 gm. Relapses occurred in two cases and the remainder have disappeared.

Geronne and Huggenberg[3] report ten cases in which a plus reaction became negative in from four to ten weeks. In four cases it remained positive, one after fifty-six days; and one after seventy days. In twenty-five cases observed for less than four weeks only six became negative.

Michaelis[4] treated 110 patients and observed only three relapses. He states that the serum reaction may become negative within a period from two to ten weeks after the injection. He observed in some instances a strengthening of the reaction after treatment, although the clinical symptoms were disappearing.

Fordyce[5] states that the results of the Wassermann test after "606" have varied within wide limits but in general a change occurred in from four to five weeks. The earliest change from a positive to a negative reaction observed by him was in six days after the injection, but in another case, after two injections, the reaction did not become negative until fifty-two days. Another case, after two injections, was still positive after seventy-four days and another after 102 days. He says that "several cases showed alternating negative and positive phases."

Herxheimer[6] records the results of 789 treated cases of which thirty-three relapsed in a period of five months. Many of his patients disappeared before a negative reaction was obtained. He observed a negative reaction in two primary cases after seven and twenty days, while four cases which were negative before the treatment became positive afterwards. Of thirty secondary cases that became negative after treatment, five became negative in from one to two weeks, the others at later periods. In seven latent cases, three became negative in from eight to fourteen days.

Weintraud[7] reports that in only thirty-seven out of seventy-seven patients, did the Wassermann reaction become permanently negative, and that in three cases it remained positive after three injections of arsenobenzol.

TABLE 1.—RESULTS OF COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN (FAVENTO)

Stage of Disease	Remained Positive	Became Negative	—Time of Disappearance of Reaction in Weeks— 1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Primary	0	15	1	4	2	3	4	0	0	1
Secondary	12	16	1	4	2	3	3	3	0	0
Tertiary	4	1	0	0	1	0	0	0	0	0
Totals	16	32	2	8	5	6	7	3	0	1

Favento[8] records very carefully the serologic data in forty-eight cases of lues in which salvarsan was used, Table 1 giving his results.

It will be observed that the majority of his cases became negative in from two to five weeks after the injection. Some of his positive cases were only observed for three or four weeks and, therefore, may have become negative later.

3. Gerrone and Huggenberg: Berl. klin. Wchnschr., 1910, xlvii, 28.
4. Michaelis, L.: Berl. klin. Wchnschr., 1910, xlvii, 1195.
5. Fordyce, J. A.: New York Med. Jour., 1911, xcii, 897.
6. Herxheimer, G.: Deutsch. med. Wchnschr., 1910, xxxvii, 1517.
7. Weintraud, C.: Med. Klin., 1910, xliii, 183.
8. Favento, A.: München. med. Wchnschr., 1910, lvii, 2080.

Noguchi[9] has recently published a very valuable serological analysis of 102 cases, in which the patients were treated with salvarsan. He states that more than half of the number were under observation for over three months, while the remainder had been injected for four weeks. He conducted a quantitative determination of the serum reaction in each case, the blood being examined before the injection and at intervals of one day, three days, one week, two weeks, three weeks, four weeks, six weeks, eight weeks, etc., after the injection. He found that thirty cases became negative, twenty-four reduced to less than 1 antibody unit, while the remaining forty-eight cases still contain more than 1 antibody unit, giving strong positive reactions. However, a titration of the serum of these cases showed that they were decidedly reduced in antibody content, although they gave strong reactions. In 40 per cent. of the primary cases; in 37 per cent. of secondary; in 35 per cent. of tertiary; in 33 per cent. of latent; in 14 per cent. of hereditary; and in 50 per cent. of incipient tabes, the reaction became negative. The average of the negative reactions equaled 33.7 per cent. of the total 102 cases. Ten relapses were observed; six of the patients were reinjected with good results and one had a second relapse. Of the negative cases reported by Noguchi, thirty-four in number, three became negative in two weeks; ten in three weeks; eleven in four weeks; five in five weeks; four in six weeks; and one in seven weeks. His results in this respect are similar to those obtained in this laboratory.

It will be noted that there is the greatest variation in the results obtained by different observers, and the number of cases which have been reported serologically is very small when compared with the vast number in which salvarsan treatment has been used. The difference in results may be explained by the class of patients treated by different observers, the amount and kind of previous mercurial treatment, and, perhaps, by the technic employed in making the tests.

THE DISAPPEARANCE OF THE REACTION IN RABBITS INFECTED WITH LUES AND YAWS

Through the kindness of Captain Nichols of the Army Medical Corps, I have recently had the opportunity of testing rabbits experimentally infected with lues and yaws, and of observing the complement fixation curve as shown by the titration of the serum of these animals, as regards its complement fixation qualities. Table 2 illustrates the results obtained in an animal infected with lues and Table 3 in one infected with yaws; these well show the gradual increase in the anti-body strength of the serum and the disappearance of the positive reaction after the administration of salvarsan.

An examination by Captain Nichols of Rabbit 39, infected with lues, demonstrated the presence of spirochetes on January 19, but the Wassermann test was not positive, even with 0.2 c.c. of serum, until January 23. From this time it gradually increased in strength until February 6, at which time 0.05 c.c. of the serum gave a double-plus reaction. At this time Captain Nichols administered intravenously 0.02 gm. of salvarsan per kilo and the reaction became negative on January 13, one week

9. Noguchi, H.: Serum Diagnosis of Syphilis, Ed. 2, Philadelphia, 1911.

after treatment. It is interesting to observe that the reaction diminished in strength on the 8th, and increased in strength on February 10, after treatment.

In Rabbit 44, infected with yaws, the spirochetes were demonstrated by Captain Nichols on January 21, but the Wassermann test did not become positive until January 30. On February 6, when 0.05 c.c. of the serum gave a double-plus reaction, 0.02 gm. of salvarsan per kilo was administered intravenously by Captain Nichols, and on February 13 the reaction became negative, one week after treatment. Here again it is interesting to observe a diminution in the strength of the reaction two days after treatment, an increase four days after treatment, and a final disappearance three days later. Similar phenomena have been noticed in human subjects, a negative reaction becoming positive after treatment or weak reactions becoming strong for a short period after the administration of salvarsan. Ehrlich believes that such changes in the reaction are due to the reaction of the tissues to poisons liberated by the destruction of the spirochetes.

TABLE 2.—RESULTS OF COMPLEMENT FIXATION TEST BEFORE AND AFTER TREATMENT WITH SALVARSAN IN RABBIT 39, INFECTED WITH LUES*

Amount of Serum	Date of Tests 1/23	1/27	1/30	2/6	2/8	2/10	2/13	2/18
0.05 c.c.	—	+	+	++	—	+	0	—
0.10 c.c.	—	++	++	++	±	++	—	—
0.15 c.c.	0	++	++	++	±	++	0	—
0.20 c.c.	++	0	++	++	±	++	—	—

* Spirochetes found in testicular lesion Jan. 19, 1911; 0.02 gm. salvarsan per kilo administered intravenously Feb. 6, 1911.

TABLE 3.—RESULTS OF COMPLEMENT FIXATION TESTS BEFORE AND AFTER TREATMENT WITH SALVARSAN IN RABBIT 44, INFECTED WITH YAWS*

Amount of Serum	Date of Tests 1/23	1/30	2/2	2/6	2/8	2/10	2/13	2/17
0.05 c.c.	—	—	++	++	—	—	—	—
0.10 c.c.	—	±	++	++	—	±	—	—
0.15 c.c.	—	+	++	++	+—	+	—	—
0.20 c.c.	—	++	++	++	+—	++	—	—

* Spirochetes found in lesion Jan. 21, 1911; 0.02 gm. salvarsan per kilo administered intravenously Feb. 6, 1911.

The results in this laboratory of the complement fixation tests in experimentally infected animals before and after treatment with salvarsan have been perfectly consistent throughout and prove indubitably the specific action of this drug on the spirochetes of syphilis and yaws.

TECHNIC AND GENERAL RESULTS

The technic used in making the tests in this laboratory is largely that recommended by Noguchi. A human hemolytic system has been used, the amboceptor being obtained from rabbits immunized against human

red corpuscles. As antigen we have used an extract of luetic fetal liver in absolute alcohol and the serum tested has always been inactivated. As we receive our specimens from army posts, many of them located at considerable distances from the laboratory, we use only inactive serum and for this reason have preferred an alcoholic extract as antigen. Guinea-pig serum has been used for complement. One cubic centimeter of a 1 per cent. suspension of red corpuscles is used for the antigen and control tubes. The technic of making the test will not be considered, as it is familiar to all who are interested in the Wassermann reaction.

Our tests have been controlled by repeated tests made at the same time on known clinical cases and the results have always been consistent.

At the present writing complement fixation tests are being made in this laboratory on over 700 soldiers who have been treated with salvarsan, but I have only considered the results in 225 cases, for the reason that the remainder have not been observed for a sufficient time for the data to be of definite value. Of the cases reported on all have been observed for at least eight weeks since the administration of the drug and most of them for a longer period.

Of the 225 cases reported 164, or 72.8 per cent., became negative and sixty-one, or 27.1 per cent., have remained positive. Of the 164 cases which became negative, twenty-four, or 14.6 per cent., have relapsed; forty-three have remained negative for two months; forty-one for two and one-half months; twenty for three months; seven for four and one-half months; eleven for five and one-half months; seven for six months, and six for seven months. It is probable that some of these cases will relapse later, but it is not believed that relapses will occur in a very large proportion of them.

A number of important factors must be considered in order to understand the exact value of these data. The number of cases which remain positive, or become negative after the administration of salvarsan is of little practical significance unless we are informed as to the stage of the disease in which the drug is administered; the intensity of the positive reaction; the method of administration, and the amount and kind of previous mercurial treatment. In view of the importance of these factors, I have endeavored to give a complete analysis of the cases in these respects, and I believe that the real effect of treatment with salvarsan on the complement fixation test can be accurately ascertained only when such an analysis is made. In the literature dealing with this subject but little attention seems to have been paid to the factors which I have mentioned, and therefore much of it is comparatively valueless.

THE STAGE OF THE DISEASE IN RELATION TO THE DISAPPEARANCE OF THE REACTION

The results obtained in this laboratory show that the immediate effect of treatment with salvarsan on the complement fixation test is much influenced by the stage of the disease. In Table 4 is given an analysis of the cases reported, showing the number becoming negative and remaining positive in the various stages of lues. The data are based on the results of one injection of salvarsan in all but a few cases, the dose employed varying from 0.5 to 0.8 gm.

TABLE 4.—THE RESULT OF TREATMENT WITH SALVARSAN ON COMPLEMENT FIXATION IN THE VARIOUS STAGES OF LUES

Stage of Disease	No. of Cases	Became Negative	Per Cent.	Remained Positive	Per Cent.	Relapsed	Per Cent.
Primary	31	25	80.6	6	19.4	3	12
Secondary	135	100	74	35	25.9	15	15
Tertiary	22	12	54.9	10	45	2	16.6
Latent	37	27	72.9	10	27	4	14.8
Totals	225	164	72.8	61	27	24	14.6

It will be observed from a consideration of the table that of thirty-one primary cases 80.6 per cent. became negative, while 12 per cent. relapsed. In the secondary cases 135 in number, 74 per cent., became negative, of which 15 per cent. relapsed. In the tertiary cases twenty-two in number, 54.9 per cent., became negative, of which 16.6 per cent. relapsed, and in the latent cases thirty-seven in number, 72.9 per cent. became negative and 14.8 per cent. relapsed. It is thus evident that the best results were obtained, as regards the disappearance of the reaction, in the treatment of patients in the primary stage and the most unfavorable in the treatment of patients in the tertiary stage. In latent cases the results are apparently somewhat better than in the secondary cases, and it is interesting to note the gradual decrease in the efficacy of the treatment the older the active stage of the disease. The results obtained are as might be expected and indicate the value of early treatment of luetic infections.

The time of disappearance of the reaction in the cases which became negative has also varied with the stage of the disease. In Table 5 is given the date of disappearance of the reaction in weekly periods correlated with the stage of the infection.

It will be noted that, considering the total number of cases, the greatest number became negative during the second, third and fourth weeks, that a considerable number became negative one week after injection, and that, in our experience, none of the cases became negative after eight weeks. I believe that unless the reaction becomes negative within this time it will not become so later, in the vast majority of cases, and

that a positive reaction after this period should always be considered an indication for further treatment.

In regard to the time of disappearance of the reaction in relation to the stage of the disease, it will be noted that the best results were obtained in the tertiary stage, no less than nine of the twelve tertiary cases becoming negative within two weeks, and that four weeks was the longest time after treatment in which the reaction became negative at this stage of the disease. In the secondary cases the reaction disappeared most frequently during the second, third and fourth weeks, while the longest period was eight weeks. In the primary cases thirteen of the twenty-five cases became negative within two weeks, while five weeks was the longest period after treatment that the reaction became negative. In latent cases the majority became negative during the second, third, fourth and fifth weeks, and no case became negative after six weeks.

TABLE 5.—THE RELATION OF THE STAGE OF LUES TO THE TIME OF DISAPPEARANCE OF COMPLEMENT FIXATION, AFTER TREATMENT WITH SALVARSAN

Stage of Disease	No. of Cases	Time of Disappearance of Reaction: 1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Primary	25	2	11	7	4	1	0	0	0
Secondary	100	10	24	24	17	10	10	4	1
Tertiary	12	3	6	2	1	0	0	0	0
Latent	27	2	6	4	5	6	4	0	0
Totals	164	17	47	37	27	17	14	4	1

The favorable results obtained in the tertiary cases, as regards the disappearance of the reaction, coincide with the remarkable influence of salvarsan on the lesions of this stage of the disease, as described by many clinicians, and they would appear to indicate that unless the reaction becomes negative within a month the majority of the patients require further treatment. In considering our results in this stage of the disease, it should be remembered that almost all of the patients had received more or less vigorous mercurial treatment, which undoubtedly had weakened the infection and thus led to an early disappearance of the reaction after the administration of salvarsan. In fact, in the majority of our cases of secondary, tertiary and latent lues mercurial treatment had been administered and the effect of this on the disappearance of the reaction will be considered later.

THE RELATION OF THE INTENSITY OF COMPLEMENT FIXATION TO THE DISAPPEARANCE OF THE REACTION

From the study of the intensity of the reaction in the cases here reported on, it is apparent that the stronger the reaction the smaller the number of cases which become negative. In the tables given in this

paper a double-plus reaction indicates complete inhibition of hemolysis, a plus reaction at least 50 per cent. of inhibition, and a plus-minus reaction less than 50 per cent. of inhibition. Classified in this way the relation of the intensity of the reaction to the time of disappearance is illustrated in Table 6.

TABLE 6.—THE RELATION OF THE INTENSITY OF COMPLEMENT FIXATION TO THE RESULTS OF TREATMENT WITH SALVARSAN

Character of Reaction	No. of Cases	Became Negative	Per Cent.	Remained Positive	Per Cent.	Relapsed	Per Cent.
++	119	79	66.3	40	33.6	13	16.4
+	71	57	80.2	14	19.7	7	12.2
±	35	28	80.	7	20.	4	14.2
Totals...	225	164	72.8	61	27.1	24	14.6

An analysis of this table shows that of 119 cases in which the reaction was double-plus 66.3 per cent. became negative, of which number 16.4 per cent. relapsed. Of seventy-one cases in which the reaction was plus 80.2 per cent. became negative, of which 12.2 per cent. relapsed. Of thirty-five cases in which the reaction was plus-minus 80 per cent. became negative and 14.2 per cent. relapsed. It will be observed that in the double-plus cases a smaller percentage became negative and a larger percentage relapsed than in either the plus or plus-minus cases and it would, therefore, appear that the conclusion is justified that the prognosis, as regards the disappearance of the reaction, is less favorable in cases giving a double-plus reaction. Of course, this is to be expected if the intensity of the complement fixation test is a measure of the severity of a luetic infection, but it is more difficult to explain why the percentage of disappearances is less and of relapses greater in the plus-minus cases than in those giving a plus reaction, as shown in the table, although a careful inquiry into the history of our cases indicates why this is so. Nearly half of the cases giving a plus-minus reaction were patients in the late secondary or tertiary stages of the disease in which the infection was still active, although they had been treated vigorously with mercury and the weak reaction in these cases is explained by the fact that mercurial treatment was omitted only a short time before the serum was tested. Had all of our plus-minus cases been in the primary or early secondary stage of the disease I believe that the percentage of disappearance would have been higher than is indicated in the table, while the relapses would have been fewer in number. The relation which the intensity of complement fixation bore to the actual time of disappearance of the reaction in the 164 cases which became negative is shown in Table 7.

This table shows that most of the cases giving a double-plus reaction became negative during the second, third and fourth weeks after treatment, the greatest number during the second week, but that no less than eight became negative during the first week after treatment. The results were similar in the cases giving a plus reaction, although a smaller number, proportionately, became negative in the first week. As would be expected the cases giving a plus-minus reaction showed the largest proportion becoming negative in the first week but some did not become so until the fifth and sixth week. The quickest results were obtained in the plus-minus cases, considered as a whole, while the results in the double-plus and plus cases were practically the same.

TABLE 7.—THE RELATION OF THE INTENSITY OF COMPLEMENT FIXATION TO THE TIME OF DISAPPEARANCE OF THE REACTION AFTER TREATMENT WITH SALVARSAN

Character of Reaction	No. of Cases	Time of Disappearance of Reaction: 1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
++	79	8	22	18	13	8	6	4	0
+	57	2	16	14	11	6	7	0	1
±	28	7	9	5	3	3	1	0	0
Totals..	164	17	47	37	27	17	14	4	1

The early disappearance of the reaction in the double-plus cases was largely due to the fact that many of these were primary and secondary cases, some of which had received previous mercurial treatment, and the amount and kind of such treatment must always be considered in interpreting the real meaning of early disappearances of the reaction.

The relation of the stage of the disease and the intensity of the reaction to the time of its disappearance after treatment with salvarsan is shown in Table 8.

In analyzing this table it is necessary to consider the intensity of the reaction in relation to its disappearance in each stage of the disease. Of the twelve primary cases giving a double-plus reaction 83.3 per cent. became negative, of which 30 per cent. relapsed; of the seventy-six secondary cases giving a double-plus reaction 63.1 per cent. became negative, of which 18.9 per cent. relapsed; of the ten tertiary cases with a double-plus reaction 40 per cent. became negative and 50 per cent. relapsed, and of the twenty latent cases giving a double-plus reaction 70 per cent. became negative, of which 14.2 per cent. relapsed.

Considering these cases as a whole it will be observed that the best results, as regards the disappearance of the reaction, were obtained in the primary stage and the poorest in the tertiary stage, while better results were obtained in the secondary stage than in latent infections. When

relapses are considered, however, the best results were obtained in the latent cases and the poorest in the tertiary cases; the secondary stage gave better results as regards relapses than the primary and this was not due, as might be thought, to either the method of the administration of the drug or to the dosage.

TABLE 8.—RELATION OF THE STAGE OF LUES AND THE INTENSITY OF THE COMPLEMENT FIXATION REACTION TO ITS DISAPPEARANCE AFTER TREATMENT WITH SALVARSAN

Stage of Disease and No. of Cases	Character of Reaction	Became Negative	Per Cent.	Remained Positive	Per Cent.	Relapsed	Per Cent.
Primary	++	10	83.3	2	16.6	3	30
31 cases	+	10	83.3	2	16.6	0	0
	±	5	71.4	2	28.5	0	0
Secondary	++	48	63.1	28	36.8	9	18.9
135 cases	+	39	86.6	6	13.3	5	12.8
	±	13	92.8	1	7.1	1	7.6
Tertiary	++	4	40.	6	60.	2	50.
22 cases	+	5	55.5	4	44.4	0	0
	±	3	100	0	0	0	0
Latent	++	14	70	6	30	2	14.2
37 cases	+	4	50	4	50	1	25
	±	9	100	0	0	1	11

Considering the cases giving a plus reaction the largest percentage of negative results occurred in the secondary stage, the smallest in the latent stage, while better results were obtained in the primary stage than in the tertiary. As regards relapses, none occurred in the primary or tertiary stages, while in the secondary stage 12.8 per cent. relapsed and in the latent cases 25 per cent.

Of the cases giving a plus-minus reaction the table shows that the best results were obtained, as regards the disappearance of the reaction, in the tertiary and latent cases, while the poorest results were obtained in the primary cases. As regards relapses none occurred in the primary or tertiary cases, but 7.6 per cent. relapsed in the secondary stage and 11 per cent. of the latent cases. In the cases in the tertiary and latent stage giving a plus-minus reaction the patients had received vigorous mercurial treatment before the administration of salvarsan, which undoubtedly explains the disappearance of the reaction in all of the cases. The patients who relapsed in the secondary stage had received no previous treatment, while the one patient who relapsed in the latent stage developed symptoms a few days after the reaction became negative.

From the data submitted it is evident that the intensity of the reaction in the various stages of the disease is of considerable prognostic import. Thus better results are obtained, as regards the disappearance of the reaction, in the primary cases giving a double-plus reaction than in the secondary, but the chances of a relapse are almost twice as great in the primary as they are in the secondary. It is also interesting to note that the plus-minus cases give a larger percentage of disappearances in

the secondary than in the primary stages of the disease, but that the chances of a relapse are greater in the secondary stage. The prognosis, as regards the disappearance of the reaction and the occurrences of relapses, is most unfavorable in the tertiary cases which give a double-plus reaction.

RELATION OF THE METHOD OF ADMINISTRATION OF SALVARSAN TO THE DISAPPEARANCE OF THE COMPLEMENT FIXATION REACTION

I had hoped to be able to give some data regarding the relation of the dosage of salvarsan to the time of disappearance of complement fixation, but in the cases analyzed the dosage has varied so little that no conclusions can be drawn regarding this phase of our subject.

The method of administration, however, had much to do with the disappearance of the reaction as will be seen on consulting Table 9. The methods used in the cases reported were as follows: Injection of the neutral suspension of the drug; intramuscular injection of the alkaline solution; intravenous injection, and combined intramuscular and intravenous injections.

TABLE 9.—VARIOUS METHODS OF ADMINISTRATION OF SALVARSAN IN RELATION TO THE DISAPPEARANCE OF COMPLEMENT FIXATION IN LUES

Method of Administration	No. of Cases	Became Negative	Per cent.	Remained Positive	Per cent.	Relapse	Per cent.
Neutral suspension	9	7	77.7	2	22.2	5	71.4
Alkaline Sol. Intramuscular	150	118	78.6	32	21.3	8	6.7
Intravenous	30	16	53.3	14	46.6	6	37.5
Combined Intramuscular and Intravenous	36	23	63.8	13	36.1	5	21.7
Totals	225	164	72.8	61	27.1	24	14.6

Neutral Suspension.—The neutral suspension of salvarsan was used in nine cases, of which seven became negative and five relapsed. Thus, while the percentage becoming negative was quite large, the percentage of relapses (71.4 per cent.) was enormous. It must be admitted that, as a rule, small doses were used, varying from 0.3 gm. to 0.5 gm., but even taking this into consideration it is evident that the method gives poor results when compared with any of the others mentioned. In justice to the method, however, it should be stated that the two cases which did not relapse, are still negative after a period of nearly ten months.

Intramuscular Injection.—The intramuscular injection of the alkaline solution of salvarsan gave the best results, as regards the disappearance of the complement fixation test, in the cases which are here analyzed. Of the 150 cases so treated 78.6 per cent. became negative, of which only 6.7 per cent. relapsed, and as some of the cases which remained positive have only been observed for a period of four weeks it

is probable that the percentage of disappearance will become greater within the next two or three weeks, but this may also be true as regards the percentage of relapses. The dose of salvarsan varied from 0.5 gm. to 0.6 gm.

Intravenous Injection.—The intravenous method was used in thirty of the cases reported, of which 53.3 per cent. became negative and 37.5 per cent. relapsed.

Seven of the cases were given 0.5 gm. of salvarsan, repeated in one week, and of these six became negative, one stayed positive and one relapsed. Four were given 0.6 gm. once only, of which one became negative and four remained positive. Nineteen were given 0.5 gm. once only, of which nine became negative, ten remained positive and five relapsed. The best results were obtained with two intravenous injections given one week apart.

Combined Intramuscular and Intravenous Injections.—This method was used in thirty-six cases, of which 63.8 per cent. became negative and 21.7 per cent. relapsed, thus giving better results than the intravenous alone, but not as good as the intramuscular method. The dosage employed in the combined method was as follows: 0.2 gm. intramuscular + 0.4 gm. intravenous; 0.3 gm. intramuscular + 0.3 gm. intravenous; and 0.6 gm. intramuscular + 0.3 gm. intravenous. The best results were obtained with the latter dosage, 50 per cent. of the ten cases so treated becoming negative, none of which have relapsed.

A few patients were treated with an intravenous, followed by an intramuscular, injection, but the number is too small to warrant any conclusions regarding the efficacy of this method of treatment.

The period intervening between the administration of the drug by the several methods and the disappearance of the reaction is given in Table 10.

TABLE 10.—THE TIME OF DISAPPEARANCE OF THE COMPLEMENT FIXATION REACTION AFTER TREATMENT WITH SALVARSAN BY VARIOUS METHODS

Method of Administration	No. of Cases	Date of Disappearance in Weeks: 1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Neutral suspension	7	1	4	2	0	0	0	0	0
Alkaline sol. intramuscular	118	12	31	27	18	14	12	3	1
Intravenous	16	3	9	3	1	0	0	0	0
Combined intramuscular and intravenous	23	1	3	5	8	3	2	1	0
Totals	164	17	47	37	27	17	14	4	1

This table is of interest as showing the relative rapidity of the disappearance of the reaction after the several modes of treatment. It will be observed that the reaction disappeared less rapidly when intra-

muscular injections were used than when the drug was given intravenously. The great differences in the rapidity of the disappearance of the reaction after treatment with salvarsan are due to numerous factors, some of which are capable of explanation, while others are still unsolved. The situation of the spirochetes, the rate and amount of absorption of the drug and the character and severity of the infection, must all have something to do with the time of disappearance, while the existence of strains of spirochetes, which may be more or less resistant to the drug, a question still undecided, may also explain the slow disappearance of the reaction in certain cases. If, as Ehrlich believes, the fixation reaction may be produced by tissue changes which occur in answer to irritation brought about by the destruction of the spirochetes, it is easy to explain the delayed disappearance of the reaction by a slow elimination of these irritating products. When elimination is rapid, either because the amount of irritating substance is small, or the tissues concerned in elimination are very active, the reaction will disappear quickly, while, if the contrary is true, elimination will be slow and the reaction will persist for a considerable period.

In the intravenous injections twelve of the sixteen negative cases became so within two weeks, while the longest period from the time of the administration of the drug to the disappearance of the reaction was one month. One would naturally expect that the reaction would disappear more rapidly after intravenous injections than after intramuscular and this is borne out by our data. The fact remains, however, that some of these cases did not become negative for three or four weeks, and it is difficult to explain this on any other assumption than that the persistence of the reaction was due to the slow elimination of substances derived from the dead spirochetes or produced by the reaction of the tissues to them. When the drug is given by the intramuscular method it is absorbed slowly, exerting its action for days or perhaps weeks and killing the spirochetes by "the instalment plan" as it were, whereas when it is given intravenously it is absorbed and eliminated rapidly, and any destructive action on the spirochetes must occur in a comparatively short time. In the first case the elimination of the substances which Ehrlich believes have to do with the production of the reaction is gradual, because the spirochetes are being continually destroyed, whereas in the second cases these substances will be eliminated more rapidly because the parasites are all killed within a comparatively short time. The elimination may take some weeks even when the drug is given intravenously, but it will never take so long as when it is given by the intramuscular method, other things being equal. This theory would appear to be contradicted by the results obtained in the cases treated with the neutral suspension, but these cases were very few in number and, therefore, of little value as an argument against the theory.

RELATION OF PREVIOUS MERCURIAL TREATMENT TO THE DISAPPEARANCE OF COMPLEMENT FIXATION AFTER SALVARSAN

Previous treatment with mercurials has considerable effect on the disappearance of the complement fixation reaction after treatment with salvarsan. This is especially noticeable during certain stages of luetic infection and should always be considered in interpreting the results of various observers as regards this question. As a rule the reaction disappears more quickly in patients who have been subjected to mercurial treatment for some time than in those who have not, and the chances of relapse are less, although, as will be seen, relapses have occurred in patients previously well treated with mercury.

In the 225 cases reported 110 patients had received no treatment previous to the use of salvarsan. Of these eighty-two, or 74.5 per cent., became negative; twenty-eight, or 25.4 per cent., remained positive, and ten or 12.2 per cent. relapsed.

There were seventy-five cases in which a definite history of mercurial treatment was obtained before salvarsan was administered. Of these sixty-three, or 84 per cent., became negative; twelve, or 16 per cent., remained positive, and seven, or 9.3 per cent., relapsed.

From these figures it is evident that better results were obtained in the patients who had previously had mercurial treatment, for not only a larger proportion of the cases became negative, but a smaller proportion relapsed.

The relation of the stage of the disease in patients who had not received previous mercurial treatment to the disappearance of the reaction after salvarsan is shown in Table 11, while in Table 12 is shown the relation of the stage of the disease to the disappearance of the reaction in the patients who had received previous mercurial treatment.

TABLE 11.—THE RELATION OF THE STAGE OF LUES TO THE DISAPPEARANCE OF THE COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN IN PATIENTS WHO HAD RECEIVED NO PREVIOUS MERCURIAL TREATMENT

Stage of Disease	No. of Cases	Became Negative	Per cent.	Remained Positive	Per cent.	Relapsed	Per cent.
Primary	27	22	81.4	5	18.5	2	9
Secondary	67	48	71.6	19	28.3	8	16.6
Tertiary	8	5	62.5	3	37.5	0	0
Latent	8	7	87.5	1	12.5	0	0
Totals	110	82	74.5	28	25.4	10	12.2

In the primary stage, in patients previously untreated, twenty-two, or 81.4 per cent., became negative, while two, or 9 per cent., relapsed, as shown in Table 11. In none of the primary cases were the patients

given mercurial treatment prior to the administration of salvarsan, so that this column remains empty in Table 12.

TABLE 12.—THE RELATION OF THE STAGE OF LUES TO THE DISAPPEARANCE OF THE COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN IN PATIENTS WHO HAD RECEIVED PREVIOUS MERCURIAL TREATMENT

Stage of Disease	No. of Cases	Became Negative	Per cent.	Remained Positive	Per cent.	Relapsed	Per cent.
Primary	0	0	0	0	0	0	0
Secondary	44	39	88.6	5	11.3	5	12.8
Tertiary	13	8	61.5	5	38.4	0	0
Latent	18	16	88.8	2	11.1	2	12.5
Totals	75	63	84.	12	16.	7	9.3

There were sixty-seven patients in the secondary stage of the disease who had not received mercurial treatment before salvarsan was administered. Of these 71.6 per cent. became negative and 16.6 per cent. relapsed. There were forty-four cases in the secondary stage which had received previous mercurial treatment, of which 88.6 per cent. became negative, while 12.8 per cent. relapsed. It is thus evident that better results were obtained in the secondary stage of the disease in the cases which had previously had mercurial treatment.

Eight patients in the tertiary stage who had not received previous mercurial treatment were tested; of the cases 62.5 per cent. became negative, while none relapsed. Thirteen patients in the same stage of the disease, which had received mercurial treatment, were tested, of which 61.5 per cent. became negative, none of which relapsed. Though the figures show a slight increase in the percentage of negative results in the untreated patients I believe that this is only apparent and that if the same number of patients in both classes had been treated the results would have been in favor of those who had received previous mercurial treatment.

Considering the latent infections eight patients were tested who had received no previous mercurial treatment; of these 87.5 per cent. became negative and none relapsed, while of eighteen patients who had received previous mercurial treatment 88.8 per cent. became negative and 12.5 per cent. relapsed. The two patients who relapsed had previously had severe lesions which were quiescent at the time the patients were treated, while in the patients who had received no mercurial treatment the histories show that the infection was of mild character. I do not believe that any conclusions can be drawn from the fact that relapses occurred in the patients treated with mercury, while none occurred in the untreated patients.

The time of disappearance of the reaction after treatment with salvarsan in various stages of the disease in patients given previous mercurial treatment and in those who had not received such treatment is shown in Tables 13 and 14.

TABLE 13.—THE TIME OF DISAPPEARANCE OF THE COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN IN PATIENTS WHO HAD RECEIVED NO PREVIOUS MERCURIAL TREATMENT

Stage of Disease	No. of Cases	Date of Disappearance of Test in Weeks: 1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Primary	22	2	12	3	3	1	1	0	0
Secondary	48	6	11	13	6	4	6	1	1
Tertiary	5	1	2	1	0	1	0	0	0
Latent	7	1	1	1	1	2	1	0	0
Totals	82	10	26	18	10	8	8	1	1

A comparison of these tables shows that there is little difference in the rate of disappearance of the reaction in either class of patients. This fact is of interest as it supports the theory that the time of disappearance depends on the rate of elimination of the substance or substances derived from the dead spirochetes or produced by the reaction of the tissues to them, the slight difference in favor of the previously treated patients being due to the destruction of a portion of the parasites, prior to the administration of salvarsan.

TABLE 14.—THE TIME OF DISAPPEARANCE OF THE COMPLEMENT FIXATION TEST AFTER TREATMENT WITH SALVARSAN IN PATIENTS WHO HAD RECEIVED PREVIOUS MERCURIAL TREATMENT

Stage of Disease	No. of Cases	Date of Disappearance of Test in Weeks: 1 week	2 weeks	3 weeks	4 weeks	5 weeks	6 weeks	7 weeks	8 weeks
Primary	0	0	0	0	0	0	0	0	0
Secondary	39	4	10	10	8	5	2	0	0
Tertiary	8	1	3	3	0	0	1	0	0
Latent	16	0	5	3	4	2	2	0	0
Totals	63	5	18	16	12	7	5	0	0

The relative efficiency of salvarsan and mercury in causing a disappearance of the fixation reaction is strikingly illustrated in the cases of patients who had previously received mercurial treatment. Of fifty-three patients who were treated with mercury by the mouth for nine months or more before the administration of salvarsan and who gave a positive Wassermann reaction, all became negative within eight weeks after the administration of this drug. The intensity of the reaction in

these cases is shown in Table 15, together with the time of previous mercurial treatment.

TABLE 15.—THE RESULTS OF THE COMPLEMENT FIXATION TEST IN FIFTY-THREE PATIENTS WHO HAD RECEIVED MERCURIAL TREATMENT BEFORE THE ADMINISTRATION OF SALVARSAN

Method of Treatment	Time of Treatment	No. of Cases	Character of Reaction ++	+	±
Internal	9 months	17	8	7	2
Internal	1 year	19	11	6	2
Internal	2 years	11	3	7	1
Internal	3 years	6	2	3	1
	Totals	53	24	23	6

It will be observed from a consideration of Table 15 that nineteen of the patients had received mercury internally for one year, of whom eleven still gave a double-plus reaction; that eleven had received internal treatment for two years, of whom three still gave a double-plus reaction, and that six patients had received internal treatment for three years, of whom two still gave a double-plus reaction, while the remainder gave a plus or a well-marked plus-minus reaction. Comparing these results with those obtained after the administration of salvarsan, all of the cases becoming negative within eight weeks, and in a vast majority of instances after only one injection of the latter drug, the infinitely greater specific action of salvarsan is clearly demonstrated.

It is generally admitted that the most efficient method of administering mercury is by the hypodermic injection of suitable salts of the metal. Ten of the patients in whom the complement fixation test was still positive had been treated in this manner before the administration of salvarsan and the number of mercurial injections and the intensity of the reaction was as follows:

Two patients had received 7 injections and gave a double-plus reaction.
One patient had received 8 injections and gave a plus reaction.
One patient had received 9 injections and gave a double-plus reaction.
One patient had received 11 injections and gave a double-plus reaction.
One patient had received 15 injections and gave a plus reaction.
One patient had received 18 injections and gave a double-plus reaction.
One patient had received 20 injections and gave a plus reaction.
One patient had received 25 injections and gave a plus reaction.
One patient had received 30 injections and gave a plus reaction.

After one intramuscular injection of salvarsan the complement fixation test in all of these patients became negative and has remained so until the present time, most of them having been observed for from two to four months. While the previous mercurial treatment must have had some effect on the infections, perhaps rendering them more sensitive to the action of salvarsan, I think it must be admitted that the results amply demonstrate the superior specific action of the latter drug.

DISCUSSION OF RELAPSES

It has been stated that of the 225 cases analyzed in this paper, twenty-four, or 14.6 per cent. have relapsed. In order to understand the exact significance of these results it is necessary to consider the cases somewhat in detail.[10]

First, as regards the relation of the stage of lues to relapses. In the primary stage three of the twenty-five cases which became negative, or 12 per cent., relapsed; in the secondary stage fifteen out of 100 cases, or 15 per cent.; in the tertiary stage, two of twelve cases, or 16.6 per cent.; and in the latent stage four of twenty-seven cases, or 14.8 per cent. It will thus be seen that the prognosis as regards relapses after treatment with salvarsan is best in the primary stage and most unfavorable in the tertiary, while it is better in the latent cases than in the secondary. Of course it is yet too early to conclude that no more relapses will occur in this series of cases, but the figures are correct, at least, as regards the occurrence of early relapses.

Second, the relation of the intensity of complement fixation to relapses. The complement fixation test gave a double plus reaction before treatment with salvarsan in sixteen of the twenty-four cases which relapsed; a plus reaction in six of the cases, and a plus-minus reaction in two of the cases. Therefore, the prognosis as regards relapse varies with the intensity of complement fixation, the best results being obtained in the cases giving a plus-minus reaction and the worst in those giving a double-plus reaction. This fact is of interest as it indicates that there is some relation between the intensity of complement fixation and the resistance of lues to treatment with salvarsan. That this is true is strikingly illustrated when one correlates the stage of the disease and the intensity of the reaction with the percentage of relapses. Thus, as is shown in Table 8, the relapses occurring in the primary stage of lues were all in patients giving a double-plus reaction, no less than 30 per cent. of such patients relapsing, while no relapses occurred in patients giving a plus or a plus-minus reaction. The same is true in the tertiary cases, 50 per cent. of the patients giving a double-plus reaction relapsing, while no relapses occurred in those giving a plus or a plus-minus reaction.

In the secondary cases the largest percentage of relapses occurred in patients giving a double-plus reaction, but relapses also occurred in cases giving a plus and a plus-minus reaction, the percentage decreasing with the severity of the reaction. An apparent exception to the rule is noted in the latent cases, where 25 per cent. giving a plus reaction relapsed and only 14 per cent. giving a double-plus reaction, but there were only four patients tested who gave a plus reaction while there were fourteen tested giving a double-plus reaction, so that it is probable that had the

10. Since writing the above, the percentage of relapses has increased slightly.

same number of patients in each class been tested the results would have been similar to those obtained in the other stages of the disease.

Third, the relation of the method of administration of salvarsan to the occurrence of relapses. The percentage of relapses varying greatly with the method of administration of salvarsan.

The neutral suspension of the drug was used in nine cases, of which seven became negative and five, or 71.4 per cent., relapsed. The alkaline intramuscular injection was used in 150 cases, of which 118 became negative and eight, or 6.7 per cent., relapsed. The intravenous method was used in thirty cases of which sixteen became negative and six, or 37.5 per cent., relapsed. The combined intramuscular and intravenous method was used in thirty-six cases, of which twenty-three became negative and five, or 21 per cent., relapsed. From these data it is evident that the intramuscular injection of the alkaline solution has given the best results as regards the occurrence of early relapses and the neutral suspension the poorest, while the combined intramuscular and intravenous has given better results than the intravenous method alone. It is also evident that the neutral suspension, as recommended by Wechselmann, should be discarded as a method of administering the drug.

Fourth, the relation of previous mercurial treatment to relapses. A slightly smaller percentage of relapses occurred in the secondary cases which had received previous mercurial treatment than in those which had not, but I do not believe that any conclusions can be drawn from the data relating to this phase of the subject, as in the vast majority of cases the amount of mercurial treatment was small and apparently had but little effect as regards the occurrence of relapse. In the latent cases which had received previous mercurial treatment 12.5 per cent. relapsed, while in those which had received no mercurial treatment relapses did not occur. A much smaller number of cases belonging to the latter class were tested, however, and therefore the results are untrustworthy and general conclusions cannot be drawn from them. (See Tables 11 and 12.)

THE TIME OF OCCURRENCE OF RELAPSES AFTER SALVARSAN

In considering this portion of our subject it should be remembered that I am only able to give the data concerning the relapses which have occurred in from one to six months after treatment and that the large majority of negative cases have only been observed for three months since the reaction became negative. It is more than probable that some of these cases will relapse later, but the results obtained indicate that the majority of relapses occur within eight weeks after the reaction becomes negative and that comparatively few occur after three months. Table 16 shows the time of occurrence of the relapses in the twenty-four cases under discussion, the time being given in weeks and computed from the date on which the complement fixation test became negative.

TABLE 16.—TIME OF RELAPSE IN TWENTY-FOUR PATIENTS TREATED WITH SALVARSAN

Time of Relapse in Weeks	No. of Cases	Time of Relapse in Weeks	No. of Cases	Time of Relapse in Weeks	No. of Cases
4 weeks	2	9 weeks	1	16 weeks	1
5 weeks	4	10 weeks	1	22 weeks	1
6 weeks	3	11 weeks	2	23 weeks	1
7 weeks	4	12 weeks	2	.....	.
8 weeks	1	14 weeks	1	.....	.
.....	14	.....	7	.....	3

It is evident from the table that more than half of the relapses occurred within eight weeks after the reaction became negative and that twenty-one of the twenty-four patients relapsed within fourteen weeks. I believe that these results indicate that, in the vast majority of instances, a relapse will occur within six months if it is going to, and that if a previously positive Wassermann test remains negative for as long as a year after the administration of salvarsan, provided clinical symptoms are absent, a relapse will not occur. I realize that this opinion is contrary to that held by many, i. e., that several years must elapse before one can be sure that this drug really cures lues, but I believe that unless the spirochetes are destroyed clinical symptoms will appear or the complement fixation test will become positive within a year, provided mercurial treatment is withheld.

I think that most authorities would consider a patient as cured who had taken a course of mercurial treatment and whose blood gave a negative Wassermann reaction a year after the cessation of such treatment, and I can see no reason why the same standard should not hold good in the treatment of this disease with salvarsan. Indeed, the mere fact that one or two injections of this drug has been followed by as good results as three years' treatment with mercury, as regards the complement fixation test, should render this standard more conclusive in the case of salvarsan than in the case of mercury. I am aware that clinical relapses sometimes occur with a negative Wassermann reaction, but I am very sure that a patient showing neither clinical symptoms nor a positive Wassermann reaction within a year after treatment with salvarsan may be considered as cured of syphilitic infection. Exceptions may occur but they will be the exceptions which will prove the rule.

GENERAL CONCLUSIONS

From the analyses of complement fixation tests after the administration of salvarsan which are given in this paper I believe that the following conclusions may be safely drawn.

1. The best results, as regards the disappearance of the complement fixation test and the occurrences of relapses, are obtained in the treatment

of patients in the primary stage of lues and the poorest in the treatment of those in the tertiary stage.

2. The complement fixation reaction disappears somewhat more rapidly after treatment with salvarsan in the tertiary stage than in either the primary or secondary stage of the disease.

3. The reaction in our experience has disappeared during the second, third and fourth weeks after treatment in the vast majority of the negative cases.

4. The prognosis, both as regards the disappearance of the reaction and the occurrence of relapses, is most favorable in patients giving a plus-minus reaction and least so in those giving a double-plus reaction.

5. As regards the method of administration of salvarsan the best results have been obtained, in our experience, from the intramuscular injection of the alkaline solution and the poorest from the use of the neutral suspension. In justice to the intravenous method, however, it should be stated that a smaller number of cases have been tested and it may be that this method will prove as efficient as the intramuscular.

6. The complement fixation reaction disappears more rapidly after the intravenous administration of salvarsan than after the intramuscular administration.

7. As regards the disappearance of the complement fixation reaction better results were obtained in patients who had previously received mercurial treatment than in those who had not, but the time of disappearance of the reaction was little affected.

8. The great superiority of salvarsan over mercury, as a specific remedy, was shown in the rapid and apparently permanent disappearance of the reaction, after one or two injections of the drug, in patients previously treated for one, two or three years with mercurials and in whom the reaction had remained positive.

9. The complement fixation test is of the very greatest value as a guide to treatment with salvarsan and it is the only method we possess of determining whether lues is actually cured by any therapeutic agent.

Finally, I believe that the data recorded in this paper eloquently sustain Ehrlich's modest claim,[11] "that the introduction of '606' makes a considerable advance in the therapy of syphilis, an advance which is not due to accident, but to the result of systematic experimental work."

11. Ehrlich, P.: Chemotherapy, Ed. 1, New York, 1911, p. 127.

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THE IMPORTANCE OF TONUS FOR THE MOVEMENTS OF THE ALIMENTARY CANAL*

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Four years ago, during an investigation of movements of the esophagus after total vagus section, I was struck by the difference between the primary and the secondary results of the operation. The primary result, seen during the first twenty-four hours after the esophagus is isolated from the central nervous system, is apparently a complete paralysis. Food, pushed onward by the still efficient cervical gullet, accumulates in a widely distending mass in the lower esophagus and may stagnate there for hours with no indication of any reaction of the encircling wall. In a few days, however, a remarkable recovery of function occurs in the lowest part of the tube, which is provided with smooth muscle. Contraction and peristalsis now appear in this region when food accumulates. An important factor for arousing these activities seems to be the stretching of the esophageal wall. For example, in the first days of recovery, a slender mass spread along the tube may lie for some time unmoved; the addition of a second mass, which causes further distention of the wall, results instantly in contractions and peristalsis. And similarly after some of the food has been driven into the stomach, the strand that remains, now reduced to a slender mass again, lies for long periods without arousing any movements of the gullet. As days go by, the lower thoracic esophagus becomes more responsive to the presence of contained material, for the material is forced into the stomach with increasing rapidity, and even slender masses are now sufficient cause for peristalsis.[1]

What is true of the lower thoracic esophagus is also true of the stomach. If the splanchnic nerves are severed (in the cat), the normal movements of the gastro-enteric canal are not altered. If now the vagus nerves are cut, the immediate result is defective functioning. For twenty-four hours after isolating the stomach from the central nervous system,

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*Presidential address delivered before the American Gastro-Enterological Association, April 19, 1911.

1. Cannon: Am. Jour. Physiol., 1907, xix, 441.

the discharge of food is much retarded. Later there is a recovery of almost normal activity.[2]

A suggestion of the condition which makes possible the restoration of peristalsis in both the isolated esophagus and the stomach was found at autopsy of animals killed two weeks after total vagus and splanchnic section. The stomach was found in remarkable tonic contraction.[3] In two instances the diameter through most of the length ranged between 1.5 and 2 cm.—a smallness of size almost incredible when compared with the diameter of the stomach filled with food. The question at once arose as to whether this tonic contraction was not in fact fundamental to the rhythmic movements.

This suggestion was first tested by injecting material into the stomach when that organ was in different degrees of contraction. If the abdomen is opened under warm normal salt solution, sometimes the empty stomach is found large and flabby, with collapsed walls, at other times it is small and contracted. Under these different circumstances the injection of a mushy mass has quite different effects. The flabby stomach simply gives way before the pressure of the injected material, without any reaction; the tonically contracted stomach, on the other hand, begins, as soon as sufficiently distended, to exhibit peristaltic waves.

The importance of the tonic state is further attested by injecting into a vein a small dose of epinephrin (P. D. & Co.) while the gastric peristaltic waves are running. This produces complete relaxation of the stomach and a cessation of peristalsis. The pressure on the stomach contents (which measures the tonus of the neuromusculature) falls to zero. A careful record of the movements of the gastric wall in the pyloric end, with simultaneous record of intragastric pressure, shows that the pressure begins to rise in the stomach, i. e., the tonic state begins to be established, before peristaltic waves begin to travel towards the pylorus.

The importance of tonus to rhythmic activity can be demonstrated also with the excised stomach. If an inactive stomach is removed from the body, is filled with warm water, is tied at the two ends, and placed in warm oxygenated Ringer's solution, it usually shows no sign of peristalsis. If, now, a small amount of barium chlorid is added to the Ringer's solution, the stomach becomes tonically contracted and peristaltic waves are generated.

The foregoing observations on the relation of tonus and peristalsis in the stomach are amplified and elucidated by an examination of these relations in the colon. All investigators who have studied antiperistalsis

2. Cannon: Am. Jour. Physiol., 1906, xvii, 437.

3. "Tonus" is used in this paper to designate a state of more or less persistent shortening of the circular muscle of the alimentary canal.

of the colon have noted that the waves start from the narrow construction, or tonic ring, nearest the cecum; but the part played by this ring has been overlooked. Two years ago I reported that by producing a tonic ring in the proximal colon (exposed under warm normal salt solution), either by pinching or by applying a weak solution of barium chlorid, moving waves could be made to appear at will. A ring at the cecum repeatedly sends off downward-running waves; a new ring made now near the terminus of these waves starts reversed waves; and a tonic ring made midway in the proximal colon not infrequently will originate waves which pass away in both directions. These phenomena occur not only in the large intestine connected with the body, but also in the excised colon. The phenomena of the tonic ring are therefore of prime importance in explaining the occurrence of antiperistalsis of the colon and possibly also the similar peristalsis of the stomach.

The antiperistalsis of the colon and the peristalsis of the stomach are alike in presenting a series of waves following one another in rhythmic succession. They must, therefore, have a source that is rhythmically active. Careful inspection of the exposed colon over which antiperistaltic waves are passing reveals the interesting fact that the tonic ring, from which they start, pulsates, and that each pulsation sends away a moving ring of constriction.

The pulsations of the tonic ring and the discharge of waves from it are dependent on a state of tension. Thus if, while the waves are running from a ring, the fluid contents are largely withdrawn, visible waves cease. Reintroducing the fluid starts the waves again. The observation which I reported in 1901, that antiperistalsis begins whenever new material is pushed into the colon from the ilium, agrees completely with the experimental evidence that distention of the intestine is the condition for the appearance of the waves.

Mechanical stretching is well recognized as a most efficient stimulus for exciting activity in smooth muscle. The evidence already cited for the esophagus, stomach and colon, is supported by similar observations on the small intestine,[4] ureter[5] and bladder.[6] Since smooth muscle surrounds hollow organs, which gradually fill and must be emptied, the value of distention as a stimulus is obvious.

The extension of smooth muscle which evokes a contraction must not, however, be merely the elongation of non-elastic substance. This is a point which I wish especially to emphasize. When an organ with walls of smooth muscle is flaccid and toneless, distention calls forth no response. As already noted, such is the case in the isolated esophagus

4. Bayliss and Starling: Jour. Physiol., 1901, xxvi, 134.
5. Sokoloff and Luchsinger: Arch. f. d. ges. Physiol., 1881, xxvi, 467.
6. Guyon: Compt. rend. Soc. de Biol., Paris, 1900, lii, 712.

and stomach immediately after severance of the vagus nerves; such is the case in the rectum[7] and bladder[8] immediately after the nerves have been cut which supply them with tonic impulses; such is the case also in the atonic colon. I have repeatedly attempted to call forth rhythmic contractions both in the atonic stomach and in the atonic colon, by distention, but without success. Only when the muscle is shortened and resilient, i. e., in a state of tonus, does stretching result in a contraction. The tonic state, therefore, is quite as important as the internal pressure —indeed, it is the condition for the existence of that pressure. And when stretching is said to be the efficient stimulus for rhythmic contraction of smooth muscle, the statement implies that the muscle is in a condition to be *stretched.*

Moderate loads applied to smooth muscle extend it more when it is in a short state than when it is in a long state.[9] At the tonic ring of the colon, therefore, the neuromusculature, because shortened, is especially subject to distention by internal pressure. And being in a tonic state, it will respond by contraction.

A single contraction in a rhythmic series consists of almost symmetrical stages of shortening and relaxation. During the stage of shortening and the first part of the stage of relaxation there is evidence that the neuromusculature of the alimentary canal is relatively refractory to stimulation.[10] When the tonic ring, therefore, begins to contract in response to distention, it becomes non-irritable to the stimulus, i. e., to the internal pressure. It begins again to be subject to this stimulus after having reached its most contracted state and having become partly relaxed—when again readily distensible. Now on being distended by the internal pressure, the ring is stimulated and, as before, responds by contraction. Thus the neuromusculature in a tonic state responds to a distending pressure by contraction, and the refractoriness which develops during the contractile phase and the lessened irritability during relaxation assure a rhythmic response. These factors can all be reasonably invoked to explain the pulsations of the tonic ring.

The spread of the contraction from the pulsating ring along the intestine, as a wave, is probably another instance of a widely observed phenomenon in simple neuromuscular structures, the passage of the state of excitation from a contracted region to a stretched region.[11] Evidently a contraction of the tonic ring must increase internal pressure on neighboring parts of the intestinal wall. If these neighboring parts

7. Elliott and Barclay-Smith: Jour. Physiol., 1904, xxxi, 289.
8. Elliott: Jour. Physiol., 1907, xxxv, 424, 425.
9. Schultz: Arch. f. Physiol., 1903, Suppl., p. 25.
10. Ducceschi: Arch. per l. Sci. Med., 1897, xxi, 170; Magnus: Arch. f. d. ges. Physiol., 1904, ciii, 540; 1906, cxi, 152.
11. See von Uexküll: Ergebn. d. Physiol., 1904, iii$_2$, 4.

are in tonic contraction, they are thereby set in increased tension. Then distended area, the muscle rings of this area begin to contract and thus either independently, as a result of extra stretching, or because the excitation, which is manifested in pulsation of the ring, spreads into the freshly to distend the regions beyond. The wave thus passes from the pulsating ring to inactive regions of the intestine; and since the constriction trails behind it an area of lessened irritability it cannot return on its course but must always move away from its place of origin.

The precise relation between the degree of tonus and the internal pressure that results in rhythmic contraction, is difficult to define. When a tonic ring is first made in the colon, it is a deep and strong contraction and it manifests no evidence of pulsations. Only when it has to some extent relaxed does it begin to beat rhythmically. On the other hand, if the internal pressure is sufficiently increased, the waves moving along the intestine will disappear and can be seen again only when the distention is reduced. Both the tonus and the distending force, therefore, can be too great for rhythmic action.

From the foregoing evidence and discussion, it is clear that, given the state of tonus in the neuromusculature of the colon, and a locally increased tonic contraction opposing an internal pressure, the characteristic antiperistalsis can be explained. As already stated, gastric peristalsis has many features in common with colonic antiperistalsis. Can the same principles be applied to explain the rhythmic gastric movements?

The stomach when first filled has roughly a conical shape—the circumference is large at the cardiac end and progressively smaller as the pylorus is approached. If the contents are fluid or semifluid, and are subjected to the tension of the gastric musculature, the pressure throughout the contents (gravity aside) will be uniform. Every unit area of the wall will be supporting the same pressure. Obviously, then, a circumference of given width in the larger cardiac end will be subjected to greater total stress than a circumference of equal width in the smaller pyloric end.

Since the forces in the inactive stomach are in equilibrium, however, the encircling muscle of the cardiac end necessarily has to exert stronger tension than that in the pyloric end. And furthermore, since the muscular wall of the cardiac sac is thinner than that of the vestibule, there are fewer muscle fibers in equal cross-sections. The greater circumference and the weaker musculature both tend to place the cardiac region at a disadvantage. The tension of the muscle in this region, therefore, must determine the pressure in the stomach.

The necessity of tone as a condition for gastric peristalsis, and the existence of a tonic state during digestion (as shown by intragastric pres-

sure) have already been mentioned. The application to the stomach of the factors used to account for the rhythmic contractions of the colon involves first of all a consideration of the degrees of relation between tonus and internal pressure. As noted in the discussion of the activities of the colon, the internal pressure may be too slight to stimulate the tonically contracted muscle, or it may be too great. Because of the conical shape of the stomach it is quite possible for a pressure to be produced too great for the neuromusculature of the distended cardiac end and too little for that of the pyloric end. Between the large cardiac and the small pyloric ends, however, the relations between internal pressure and tonus will be intermediate, and at some point the relations will be suitable for a contractile response. The material displaced by a contraction must be accommodated in the cardiac region where the weakest muscles are working against greatest obstacles. As the contracted band relaxes, however, the tonic pressure from the cardiac end again puts it on a stretch. Thus the contraction would be repeated rhythmically at this point, for the same reasons that were given for rhythmic pulsations of the tonus ring in the colon.

Each pulsation of the adapted gastric band will send off a wave toward the pylorus. The wave will not travel in the opposite direction (towards the fundus), because the cardiac sac is too much stretched to respond; if it were not, it would itself be the site of the pulsating band.

In harmony with the preceding argument is the observation that when peristaltic waves are running on the stomach, their place of origin can be shifted towards the pylorus by increasing internal pressure, or almost to the fundus by decreasing that pressure. In the first procedure the overstretched region is extended and the pulsating circumference, having to meet a greater distending force, is moved to a region where the muscles are stronger and lie in a smaller ring. In the second procedure precisely the opposite occurs—the muscles of the cardiac end, gradually less stretched beyond their responding power, begin to contract and in consequence the pulsatile source of the waves is moved farther towards the area of weakest musculature and longest circumference.[12]

As the stomach empties, the mid-region becomes narrow. The waves then originate at the upper end of a gastric tube, at a pulsating ring which separates the tube from the cardiac sac. The ring forms a depression which has been repeatedly noted in *x*-ray photographs of the human stomach,[13] and is observable also in the exposed stomach of lower animals. In radiographs this persistent constriction has been designated the

12. Cannon: Am. Jour. Physiol., 1911, xxvii, p. xiii.
13. See Kaestle, Rieder and Rosenthal: Arch. Röntgen Ray, 1910, xv, 21-24.

"incisura cardiaca." The activity of this deepened ring can best be explained in the same terms that were used to explain the activities of the tonic constrictions of the colon.

Since the stomach when full has a conical shape, the formation of a gastric tube of fairly uniform diameter requires a greater contraction at the cardiac end of the tube than at the pyloric end. Because the cardiac incisure, at the extreme cardiac end of the tube is therefore more contracted than any other part of the stomach, it, like the tonic ring in the colon, is probably more easily distended than any other part. Distention by internal pressure causes the tonic ring to respond rhythmically. Each contraction sends off a wave towards the pylorus. And as the food is forced on into the intestine, the cardiac sac, by tonically pressing on its contents, provides more material for the waves, while helping to maintain the internal pressure necessary for the continuance of gastric peristalsis. Only after the contents, the medium for exercising internal pressure, have disappeared, does gastric peristalsis normally cease.

Distention of a tonically contracted neuromusculature explains not only the rhythmic activities of the stomach and colon, but also those of the small intestine. The contractions of the intestine can be increased, within limits, both in extent and vigor by an increase in the distending force, or if the contractions are absent they may be started by distention.[14] When a distending balloon is introduced into the intestine, the contractions are most marked in the region of greatest tension.[15] The violent segmenting activity in cases of obstruction[16] also point to distention of the gut as a cause of rhythmic contractions. Indeed rhythmic segmentation itself is an excellent example of the response of the intestine to stretching, for the contraction each time occurs in the bulging region, about midway between two previous contractions.[17]

In the esophagus, the stomach, the colon, and the small intestine, the importance of tonus has now been explained. It is the prime condition for that tension, or stretching, which has long been recognized as the most effective means of rousing contraction in viscera with walls of smooth muscle. When that tension is developed, contraction results; and if the tension persists, the contraction recurs. It recurs as soon as the neuromusculature can recover from a previous contraction. The result is that *rhythmic* activity appears—the activity most obviously characteristic of all movements of the alimentary canal. Since, therefore, the tonic state underlies all these exhibitions of rhythmicity, it is important to consider the conditions under which tonus is developed.

14. Bayliss and Starling: Jour. Physiol., 1899, xxiv, 105.
15. Bayliss and Starling: Jour. Physiol., 1901, xxvi, 134.
16. Cannon and Murphy: Am. Surg., 1906, xliii, 522.
17. Cannon: Am. Jour. Physiol., 1901, vi, 256.

When the vagus nerves are cut, the movements of the esophagus and stomach are for some time in abeyance; and even when peristalsis reappears the constrictions at first are weak and relatively ineffective. On the other hand, repeated stimulation of the vagus nerves causes an increased and more permanent tonic contraction of the gastric wall, and as the tonus increases the peristaltic constrictions increase in vigor.[18] We may conclude, therefore, that the function of the vagi is that of setting the neuromusculature in a tonic state, of making it exert a tension, so that in relation to the contents it acts as if stretched by those contents.

The evidence already adduced to show the importance of the tonic state for normal functioning is reinforced by the observation previously mentioned that when all extrinsic nerves are cut, the esophagus and the stomach develop in time, within themselves, a tonic state. Whether the vagi are present or not, therefore, the neuromusculature must be in tonus and in tension before response will occur. In all probability the vagi adapt the size of the stomach to the varying amount of food ingested. Thus, if the stomach were relaxed, these nerves might set the musculature into tension about a small amount of food which would not by itself produce any tension whatever. When these nerves are severed, however, and time is allowed for the development of an autogenic tonus, the autogenic tonus compensates by rendering the stomach so contracted that even if a small amount is swallowed the muscle is stretched and peristaltic activities are at once started.

The question now arises as to the stage in the digestive process at which vagus influences affect gastric tonus. That impulses pass down the vagus nerves to the stomach during mastication and ingestion of food was proved by Pawlow's observation on the psychic secretion of the gastric juice.[19] As already stated, repeated stimulation of the vagi results in an increased tonic state which is much more persistent than that which follows single stimulation. Since a tonic state is necessary for gastric peristalsis, and since, as we have seen, peristalsis does not appear if the vagi are cut shortly before food is eaten, the inference is that, just as there is psychic secretion, so also there is psychic tonus. At present, however, no direct evidence for this inference has been secured.

After digestion is well started, the vagus nerves can be severed without altering either the nature of gastric peristalsis or the rate at which the stomach empties itself. This statement is based on observations by means of *x*-rays, also on inspection, and on records of intragastric pres-

18. May: Jour. Physiol., 1904, xxxi, 262.

19. Pawlow: The Work of the Digestive Glands, London, 1902, p. 50.

sure when the digesting stomach was exposed under salt solution. The initial tonus (psychic?) might be aroused while food was being ingested, and might continue for a period of some minutes thereafter. Then the tonic state must be maintained by other agencies. As the above evidence, together with observations on the excised stomach, shows, the tonic state, once established at the beginning of gastric digestion, is self-supporting. And again like the psychic secretion, it maintains itself by some local mechanism.

The small intestine is also supplied with "motor" impulses by the vagus nerves. Stimulation of these nerves, in the absence of the splanchnics, results in a brief inhibitory phase, followed by a rise of tonus and a gradual increase of rhythmic contractions to an extent above the normal.[20] In all probability, therefore, the vagi act on the intestine, just as they act on the stomach, to produce a tonic condition of the neuromusculature. In this connection it is interesting to recall Magnus' experience in studying isolated pieces of intestine, that the strips beat more actively when removed from a normally-fed animal than when removed from an animal that was not digesting.

The tonus of the colon is increased by the pelvic visceral nerves which belong to the sacral autonomic system. They are distributed especially to the distal part of the colon. Nevertheless, Elliott and Barclay-Smith report that stimulation of these nerves first increases the tone of the mid-region of the large intestine, and that then antiperistaltic waves may arise in the region of increased tone.[21] Severance of these nerves causes evident disturbance of the movement of the colon. The loss of the tonic impulses results in accumulation of feces, and in weak and sluggish contractions just as is the case when the vagus impulses are removed from the esophagus and stomach.

Looking back over the evidence here adduced we see that double provision is made for the establishment of a state of tonic contraction in the alimentary neuromusculature. Almost the entire length of the digestive canal is supplied with extrinsic nerves which when stimulated cause an increase of tone and when destroyed leave the canal at first in a toneless state. And if the canal is entirely separated from the central nervous system it has a remarkable power of developing an independent tonic state. When thus isolated, the canal regains its characteristic movements only as it recovers tone. Tonus is therefore fundamental. It supplies the resiliency that causes the state of tension when the canal is filled, or establishes the state of tension when the canal is only partly filled. The state of tension is the occasion for the contraction of viscera which

20. Bayliss and Starling: Jour. Physiol., 1899, xxiv, 131.
21. Elliott and Barclay-Smith: Jour. Physiol., 1904, xxxi, 282, 283.

are walled with smooth muscle holding a nerve net. Refractoriness to stimulation during contraction, and gradually increasing irritability during relaxation, result in a rhythmic response to the condition of tension. The most characteristic feature of the movements of the alimentary canal, their rhythmicity, can thus be accounted for.

The view that tonicity of the neuromusculature of the alimentary canal is a fundamental necessity for the appearance of rhythmic movements harmonizes many diverse observations. It accounts for the failure of efficient motility in atonic states of the stomach and intestines. It gives a reasonable explanation for the existence and importance of extrinsic motor nerves. It is in agreement with the observation that tonic contraction and rhythmic peristalsis disappear together in cases of general bodily weakness, when the depleted central nervous system may be supposed to fail to deliver the necessary tonic impulses; it is also in agreement with the observation that worry, anxiety and distress stop gastro-intestinal movements, for such states, accompanied by splanchnic impulses, abolish tonus. It fits admirably with the fact that the stomach of hungry animals is strongly contracted, for then the tonic state makes the organ ready for instant action on swallowed food. Indeed I am inclined to believe, for reasons which time does not now permit me to develop, that the sensation of hunger results from tonic contraction of the empty stomach. These are only some of the conditions in which the importance of tonus for movements of the alimentary canal is manifested; doubtless other conditions will suggest themselves.

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BRILL'S SYMPTOM-COMPLEX; TYPHUS FEVER; MANCHURIAN TYPHUS*

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In 1910 Dr. Nathan E. Brill[1] published a clinical study based on 221 cases of a disease which he has observed during the last fourteen years in the wards of Mount Sinai Hospital. His definition of the disease in question is as follows: An acute, infectious disease of unknown origin and pathology, characterized by a short incubation period (four to five days), a period of continuous fever, accompanied by intense headache, apathy and prostration, a profuse and extensive erythematous maculopapular eruption; all of about two weeks' duration, whereupon the fever abruptly ceases either by crisis within a few hours or by a rapid lysis within three days, when all symptoms disappear.

Although these cases have been taken for typhoid fever by the greater number of New York physicians, yet there is no question that Brill is right in emphatically stating that this is an incorrect interpretation of the symptom-complex described. He publishes a tabular arrangement of the differences in the clinical pictures of the two diseases, which is quite convincing; more important yet is the fact that in none of the 221 cases observed was a Widal agglutination reaction obtained, and blood-cultures carried out under the supervision of Dr. E. Libman of the Mount Sinai Hospital were uniformly negative. Similar reasoning proves that the disease under discussion has nothing in common with the group of paratyphoid diseases, for in these also agglutination reactions and specific organisms have not been obtained. A committee of the Section of Medicine of the New York Academy of Medicine appointed to consider Brill's communication has agreed with Brill on these points.

Brill then considers the differentiation of his symptom-complex from typhus fever, the resemblance to which he admits, saying that "I should have felt that I had offered nothing to our nosology if it had not been proved that typhus fever had lost its virulence, that it was constantly present in a community, that it was not communicable, that when it was present epidemics of it did not occur, and that it was no longer a grave and fatal disease." "But," he adds, "with typhus fever as the great

*Read before the Section on Medicine, New York Academy of Medicine, May 16, 1911.

1. Brill, Nathan E.: An Acute Infectious Disease of Unknown Origin, Am. Jour. Med. Sc., 1910, p. 484.

masters of medicine have taught and as I have seen it, such a conception would be unjustifiable; therefore, I believe this disease not to be typhus fever."

It is my purpose to show in this paper that the conditions which Brill demands as the *sine qua non* of admitting that his clinical entity is typhus fever can be proved to exist, and that the disease in question is in no way different from a great number of typhus fever cases observed during epidemics in countries in which typhus fever is endemic or from sporadic cases observed in the United States and elsewhere. With all deference to the great masters of medicine who have differentiated typhus and typhoid fevers and have given us the typical description of the former disease, which description has been repeated constantly since in the text-books of countries where typhus fever is unknown or unrecognized, it must be noted as a serious omission on Brill's part to fail to acquaint his readers with the views of modern or recent authors who have observed cases of typhus fever while possessing all the advantages of the medical progress in differentiating other diseases from them, advantages which were absent in the time of the "great masters of medicine." The very reactions used by Brill in proving that his symptom-complex is not typhoid fever, namely, the agglutination tests and the blood-cultures, may be named among these advantages.

I was in active practice in western Russia for six years, during which I had the chance to observe three severe epidemics of typhus fever and constantly saw sporadic cases of the disease. Of course, as the etiological factor as well as the special pathology of typhus fever has not yet been discovered, it can be diagnosticated only by the clinical course, and the more I read Brill's description, the oftener I listen to discussions of the theme, the more inclined I become to identify "Brill's disease" with typhus fever. The fairly sudden onset of the affection, the fever curve, the duration of the illness, its termination, the nature of the eruption, the time of its occurrence, the intense headache, the relatively frequent occurrence of herpes labialis, the rapid convalescence, the occurrence of the disease in patients who have previously had typhoid fever, the frequent enlargement of the spleen, the complications involving the respiratory tract, all these I have seen in authentic cases of typhus fever occurring during epidemics and independently of them.

On several occasions Brill has emphasized the intense headache which dominated the clinical picture from onset to convalescence. Other observers dealing with typhus fever have laid stress on this point. Dillingham[2] states that among 560 cases of typhus, intense headache was the most constant symptom. It was either frontal, temporal or diffuse

2. Dillingham, T. H.: Diagnosis of Typhus Fever, New York Polyclin., 1893, p. 97.

over the entire head. In a sporadic case described by Cook[3] there was violent headache during the entire period of illness, the pain being characterized by the patient as "awful." To me this is one of the most striking features of typhus fever as I have observed it. I remember especially well an epidemic of typhus fever which was accompanied by an epidemic of small-pox. In the beginning of the disease, before the eruption, the mental diagnosis ran frequently thus: severe sacral pain — small-pox; severe headache — typhus fever.

In regard to the skin eruption, I have seen cases of the maculopapular type, but likewise other cases showing a roseola and petechiæ, or petechiæ alone or roseola alone. In the first communication, based on seventeen cases, Brill[4] described the eruption as a roseola. In his later communication, however, he states that at the time he committed a mistake, the eruption being maculopapular in all cases. In my opinion this retraction is not necessary; I have seen many cases of typhus fever with a roseolar eruption only, coinciding with Brill's early cases except that in two patients the eruption involved the face as well as the trunk and extremities. It should be mentioned that there are rare typhus fever cases which show no eruption at all, the diagnosis being possible only during epidemics. Biernacki[5] has described such cases and I have likewise seen them. Many of Dillingham's[2] cases had a maculopapular eruption, and the description of the eruptions observed by Clark[6] in forty cases which occurred on Blackwell's Island show many that resemble Brill's cases and those observed by me.

The affection of the respiratory tract was striking even in cases of medium gravity: conjunctivitis, coryza, bronchitis were of frequent occurrence, and these manifestations in children when the eruption was macular caused great difficulty in differentiating typhus fever from measles. In grave cases stupor was a marked feature among adults, so that catheterization, for instance, was frequently necessary even in early days of the disease; otherwise the nervous manifestations observed by me corresponded entirely with those mentioned by Brill. I have also seen cases during epidemics which showed fever and an exanthem only without any manifestations from the nervous system.

In my light and medium cases the disease lasted from ten to fifteen days, in a few cases not over a week and very rarely five days; in grave cases up to twenty-one days. The termination was usually marked by an

3. Cook, A. H.: A Case of Sporadic Typhus, Lancet, London, 1884, p. 676.

4. Brill: A Disease Clinically Resembling Typhoid Fever but Without the Widal Reaction, New York Med. Jour., 1898, p. 48.

5. Biernacki, E.: Typhus Exanthic. sine Exanthemat., Gaz. lek. Warszawa, 1894, p. 562.

6. Clark, L.: Some Observations on an Epidemic of Typhus Fever, Am. Med.-Surg. Bull., 1894, p. 647.

incomplete crisis or by a rapid lysis. If no complications occurred, patients could sit up in bed at the end of the fever and leave the bed a few days later. Thus, convalescence was usually rapid. Among complications were observed severe bronchitis, bronchopneumonia, pulmonary gangrene twice, pleurisy with effusion twice, rarely true nephritis, though febrile albuminuria was frequent. In a few cases which ran a fatal course diphtheritic sore throat appeared, usually in the beginning of the second week. Intestinal complications such as frequently occur in typhoid fever have not come under my observation. On several occasions considerable meteorism was present. In nearly all there was obstinate constipation, but in summer diarrhea was often present. Brill states that typhus fever does not occur in summer, but this statement is only partially correct; whenever there was an epidemic in winter, sporadic cases occurred in the following summer. One of the epidemics in which I was actively engaged commenced in February and lasted till August. The Berlin[7] epidemic of 1868 was not arrested until the end of July. It is usually assumed that patients are made immune by one attack of typhus fever, but I have certainly seen a repetition of the affection in the same individuals. In one case the first attack was mild, the second severe. In another instance the disease ran a medium course in both attacks.

I will now proceed to a consideration of the epidemiology of typhus fever, it being my object to present but a few features of the cases I have seen. Were I to present complete descriptions of my medium and light cases, it would amount simply to a repetition of Brill's elaborate communication.

Let us first approach the question whether typhus occurs only in epidemics, and the answer is: by no means. Typhus is endemic in many districts of Russia, so that sporadic cases are of constant occurrence there. In many other districts where hygienic conditions are very favorable, typhus fever is but little known, and if sporadic cases do occur, they are of a mild character. As examples of such localities may be mentioned the Baltic provinces of Russia and Finland. When sporadic cases running a mild course, and consequently not accompanied by any mortality, occur in large cities they are usually not recognized. These cases are generally designated as an "uncertain kind of typhus," in other words, "a disease of unknown origin." If one has observed typhus cases in the neighboring small towns, the conviction is soon forced on him that the sporadic cases in the large cities have been of the same character. Small towns are, in my opinion, in a more favorable position for the study of the various types of typhus, one of the reasons being that the entire clinical material passes through the hands of but one physician, as frequently is the case in Russia.

7. Obermeier, O.: Die ersten Fälle und der Character der berliner Fleck-typhus Epidemie von 1868, Berl. klin. Wchnschr., 1873, p. 349.

Typhus is endemic not only in Russia, but also in many other countries. Virchow[8] assumed that the endemic typhus of the Slav countries led to the epidemic outbreak in Berlin in 1867-68. Why endemic diseases do not lead to epidemics every day cannot be decided. However, according to Virchow, a special predisposition in the locality and, perhaps, the cooperation of accidental conditions may be responsible. According to Murchison,[9] many epidemics originate from local contagion which may have been preserved in an endemic way, or may have appeared because of hunger and dirt among the inhabitants.

The last epidemic in Breslau, according to Leonhardt,[10] came to an end in July, 1879. In the following years sporadic cases of typhus fever occurred, which in 1883 increased to thirty-six. In 1885-86 not a single case occurred, in 1887 and 1888 two cases each, and in 1892 one case.

In Edinburgh,[11] in the old town, typhus was practically endemic at one time. There was not a single year from 1880 to 1893 without typhus cases.

Vacher,[12] speaking of typhus epidemics in Ireland, said that the affection was not recognized for months, as the physicians did not know anything about the disease. According to him, defective medical education is responsible for this state of affairs, and no time should be lost to remedy it. Typhus, he says further, is not rare, and in large urban centers, where the medical schools are situated, sufficient cases for clinical instruction can be found if looked for.

In Italy and Bohemia the affection is likewise said to be endemic.

Occasionally in the literature there are reports of sporadic cases of typhus. In 1897, four cases were reported from San Francisco by Shanon.[13] In two of these cases the diagnosis was rejected by the local board of health, which subsequently designated them as typhoid. The competency of the physician who reported the cases could not be doubted, as he had had considerable experience with this disease in Central America. Massie,[14] a country physician, reported a sporadic case, adding that a second case had not occurred in the district. In 1897 a few cases of typhus were reported in London,[15] and in a few suburbs of the city

8. Virchow: Quoted by Obermeier (Note 7).

9. Murchison: Quoted by Obermeier (Note 7).

10. Leonhardt, M.: Ueber das Vorkommen von Flecktyphus und Recurrens in Breslau, Ztschr. f. Hyg. u. Infektionskrankh., 1897, p. 22.

11. Littlejohn and Ker: The Outbreak of Typhus Fever in Edinburgh, Brit. Med. Jour., 1898, p. 1704.

12. Vacher, T.: Typhus and Its Notification (The Lesson of an Epidemic). Pub. Health, London, 1890-91, p. 263.

13. Shanon, N. V.: Occidental Med. Times, Sacramento, 1897, p. 651.

14. Massie, T.: A Case of Typhus Fever, Brit. Med. Jour., 1898, p. 1134.

15. Dudfield, T. O.: Typhus Fever in London, Brit. Med. Jour., 1898, p. 967; Lancet, Lond., 1898, p. 1016.

there were even small epidemics. De Arellano[16] states that typhus fever is not endemic in the capital of Mexico, but is always present in a very extensive zone in the republic. From 1869 to 1891, not a month passed but cases of typhus occurred in Mexico, although epidemics in that interval have been reported only from 1873 to 1877.

These facts show that in many parts of the world typhus is endemic. The epidemic in Edinburgh, in 1899, proved that after eighteen years of immunity an epidemic can occur. From this the conclusion may be drawn that in a community typhus may be present for a long time without leading to an epidemic.

The history of typhus epidemics in New York proves that the disease occurred epidemically only after certain fairly definite intervals.

The first considerable epidemic in New York was in 1847, following the Irish famine of the same year; in 1861 the disease was again introduced by Irish immigrants, and did not finally disappear until three years had elapsed. Since that time it has been twice mildly epidemic in the city, in 1881 and again in February, 1892. In all these instances the fever was brought to this country from regions where it is endemic. In the opinion of Branan and Cheesman[17] typhus had never become endemic in New York, but has always disappeared when suitable hygienic measures were instituted.

Janes[18] asks how it is that the outbreak of typhus occurred in New York in 1881, after an absence of the disease for about fifteen years. It was believed by some at the time that it was brought by tramps from a city in a neighboring state where a number of cases had previously occurred, and this explanation seemed reasonable, although it was never shown to have been the case. He believes that in all probability the first case was a mild, unrecognized one, and was probably followed by others equally mild. This state of affairs, according to Janes, must have extended over a considerable period, until a resident physician in Riverside Hospital suspected typhus fever in one case. His diagnosis was confirmed by Dr. E. G. Janeway, at that time health commissioner. After the announcement of this case the epidemic became evident. Thus we see that Janes, eleven years previously, was not so optimistic as Branan and Cheesman. He believed that in New York typhus might be an endemic disease.

Brill's observations commenced in 1896, but one year before that, Hubbard,[19] of the Riverside Hospital, New York, reported "cases simu-

16. de Arellano, N. R.: Etiology and Prophylaxis of Exanthematicus Typhus, Am. Pub. Health Assn., Concord, 1893, p. 81.

17. Branan and Cheesman: A Study of Typhus Fever, Clinical, Pathological and Bacteriological, Med. Rec., 1892, p. 713.

18. Janes, E. H.: Typhus Fever in New York City, Am. Pub. Health Assn., 1884, p. 301.

19. Hubbard, S. D.: Cases Simulating Typhus Fever, Med. Rec., 1895, p. 21.

lating typhus." Why this author thought that his cases only simulated typhus and were not the real disease is unintelligible to me after having thoroughly studied his communication.

As an important reason for regarding the disease as "of unknown origin," that is, a clinical entity and not as typhus, Brill mentions the absence of fatal cases at the hospital. Since his communication first appeared, however, three fatal cases have been reported.

The mortality of typhus epidemics has considerably decreased through improved hygienic conditions and modern sanitation, but, of course, this mortality will always depend on the unknown "genius epidemicus," as is the case in other infectious diseases.

The Russian prison typhus still shows considerable mortality, perhaps as high as has been stated by the masters of medicine for the typhus fever in their time. *Vrach* (1909, p. 391) makes the following statement:

> Typhus in prisons is not an accidental manifestation, these institutions being the birth-place of the disease. It is the product of our prison conditions. True, the overcrowding of the prisons has not commenced yesterday, but it increases every year. Since they have never been empty, and new inmates are constantly arriving, the cells can never be thoroughly cleansed, much less disinfected when a prisoner falls ill. The prisoners starve even in the metropolitan prisons, unless they receive monetary help from outside.

Vrach (1909, p. 140) reports as follows: "A typhus epidemic broke out in a provincial prison, in which 1,317 prisoners have been crowded, although there was hardly room for 300."

Under these conditions a mortality of over 50 per cent. may be expected. In these prison epidemics, nurses and physicians succumb even at the present time. The mortality in hospitals and private houses is, however, not as appalling. I have no exact statistical material at hand from my three typhus epidemics, but I may state that the mortality was from 6 to 9 per cent. In one of my typhoid epidemics I have had a larger mortality (10 per cent.) than in the epidemics of typhus fever. This, of course, is easily explained by the fact that dietetic rules cannot be carried out as carefully in private practice among the poor, as in hospitals. Rigorous diet is not of such great importance in typhus as in typhoid fever, because in the latter intestinal perforation and hemorrhages from the bowels are to be apprehended, which is not the case in the other disease.

In eastern Prussia[20] the mortality amounted to 10.25 per cent. in the years 1868-69. Tcherepin[21] reported on the typhus epidemic in St. Petersburg during 1902 and 1903, as follows: "In a period of seven

20. Seliger: Die Flecktyphusepidemien in der städtischen Krankenanstalt, z. Königsberg, i. Pr., Berl. Klin. Wchnschr. 1888, p. 1028.

21. Tcherepin, S.: Die characteristischen Eigenthümlichkeiten der Flecktyphusepidemien in Petersburg im Jahre 1902-3, St. Petersb. med. Wchnschr., 1904, p. 52.

months 428 patients were treated in the hospital barracks. The majority of the patients belonged to the indigent classes; the mortality was 8.6 and 9.5 per cent., respectively."

In my sporadic cases there was rarely a death, as the majority ran a mild or medium course.

Dillingham[2] gives a description of "so-called typical cases" of typhus, in which recovery took place, and if they are carefully analyzed and compared with Brill's cases, the identity will be apparent. From Littlejohn's[11] statistics of endemic cases in Edinburgh it will be seen that from 1880 to 1889 the mortality was 28 per cent., from 1889 to 1898 only 14 per cent.

In less than ten years the mortality in Edinburgh was reduced by one-half. The mortality in my three typhus epidemics was small, possibly because most of my patients were Hebrews. My observations have shown that Hebrews are usually attacked by mild and medium forms of the disease and that the mortality among them is relatively lower than in other races. As most of Brill's patients were Russian Jews, the mild course and the low mortality may perhaps be explained from this fact. Of other races, a low mortality has been reported by Conseil[22] among Arabs. During the typhus epidemic in Tunis, in 1906, there was a mortality of only 5.4 per cent., and the affection showed a relatively mild course among the Arabs. For this reason the diagnosis of sporadic cases among them was difficult. Gourrier,[23] in 1903, did not have a single death in nine typhus cases among the Arabs. This opinion of the mild course of typhus fever among the Arabs is also shared by Franco.[24] These facts are perhaps of importance in Brill's cases, because his patients belonged to a race in which the course of the affection is much milder even during epidemics.

The most important argument which Brill presents is that the disease is not communicable, and up to a short time ago it was very difficult to discuss this argument. He writes:

> One of the nurses in training school, who, in December 1896, went through a severe typhoid infection, was attacked six months later with this disease, though at that time there was no other case of this disease in the hospital or training school. She was the only person I have seen developing the disease within the hospital.

Contagiousness, however, is a relative term. Such factors as unfavorable hygienic conditions and individual predisposition play an important rôle. It may surely be assumed that the contagious substance remains in the hospital and that many patients were not affected simply because they were not predisposed to the affection. This nurse had had typhoid fever

22. Conseil: Le typhus exanthémat. en Tunisie, 1906, Thèse de Paris, 1907.
23. Gourrier: Quot. from Conseil.
24. Franco, F.: Thèse de Paris, 1903-1904.

six months previously, and this may have been the determining factor. I have observed many cases of typhus fever in patients who had had typhoid in the same year. A house physician of the Mount Sinai Hospital told me that the hospital possessed the history of two members of the same family who had become infected with Brill's disease. Warren Coleman observed the affection in four members of the same family in Bellevue Hospital.[1] Dr. Lewis A. Conner told me of three sisters in the New York Hospital who almost simultaneously contracted the disease. But even all these cases do not demonstrate direct contagiousness. I do not think that contagiousness, except in the presence of unfavorable conditions or of predisposition, or both, has ever been positively demonstrated. There is to my knowledge in the entire literature only one case (this, however, is very instructive) of typhus fever transferred by inoculation from one individual to another, the author, Motschutkowski,[25] having made the following experiment on himself: From a patient suffering from typhus he obtained a little blood through a small skin incision; he inoculated himself with this and eighteen days later developed a typical typhus fever which took a similar course to that in his patient. Since this author had treated many typhus patients for four years without being affected, he concluded that typhus can be inoculated and that the infectious agent must be in the blood. I mention this case believing that it is singular in the literature.

There is hardly an infectious disease, the spreading of which depends so much on the hygienic conditions as is the case in typhus fever. Well-to-do people, or individuals who can afford the comforts of life, are not greatly subject to the infection. The disease, however, easily spreads in the dwellings of the poor and in lodging houses where there is bad air and little light.

Brill's cases were observed in the wards, not in the private pavilions of the hospital. Consequently, his cases came from the poorer classes, that is, from New York tenement houses. In buildings of this description several inmates are usually affected by the disease during epidemics,

Palatial residences, which are not secure from typhoid fever, scarlet fever and measles, are nearly always immune to typhus. In fact, during epidemics I have very rarely seen typhus among the better class of patients, and if in rare cases it did occur usually no other member of the family became infected, although no precautions in the way of isolation were taken. Whoever is acquainted with these facts will not be surprised that in the well-ventilated wards of the Mount Sinai Hospital, and other equally well-equipped hospitals of New York, nurses, physicians and other patients have not been infected.

In my town, in a small, well-equipped hospital, where during epidemic years there were many patients with typhus fever, as well as a few in

25. Motschutkowski: Ueber die Ueberimpfung der Flecktyphus, St. Petersb. med. Wchnschr., 1900, p. 30.

other years, I never observed infection of nurses or patients. I, myself, have been infected with typhoid and Asiatic cholera, but never with typhus, notwithstanding the fact that I came in close contact with patients during three epidemics.

Strümpell[26] says: "In the well-ventilated barracks of the Leipsic Hospital cases of infection with typhus fever of physicians, nurses or patients have only been isolated."

Yet Strümpell speaks of epidemics, Brill of sporadic cases of "acute infectious disease." Wyckoff,[27] referring to the epidemic of typhus fever in New York in 1892, reports "that the medical and inspecting staffs were spared." Of the nurses and sanitary police three or four only have contracted the fever and no one died.

According to Littlejohn,[11] during an outbreak of typhus fever in Edinburgh, seventy-eight cases were treated at the hospital in a few months. Not one of the staff who came into contact with the disease caught the fever. Statistics prove that typhus is not more common amid the dwellers of the houses in the vicinity of the Juarez Hospital in Mexico, than among those who dwell in other quarters of the city. According to Arellano,[16] at the said hospital, where there are always a great number of typhus cases, the disease does not spread among the patients who are in other wards of the same establishment.

Want of cleanliness, insufficient food or food of bad quality, fatigue and moral depression are, according to Brena, predisposing factors in the spread of typhus.

The disease has undoubtedly lost its virulence on account of good hygienic conditions and thorough modern sanitation. It is no longer to any extent a disease of important centers of population served by efficient sanitary staffs.

It now scarcely ever attacks the well-to-do who live in good houses. The fear of its assuming a wide-spread epidemic character no longer exists. It cannot at the present time even be called a prominent danger to armies in the field, or to beleaguered towns. But the disease still exists.

The diagnosis of typhus, according to Mahon,[29] is seldom made, or made only when the disease has become more or less epidemic. The name "influenza" covers a multitude of diseases.

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26. Strümpel, A.: Specielle Pathologie und Therapie der inneren Krankheiten, 1889, i, 43.

27. Wyckoff, R. M.: The Recent Incursion of Typhus Fever at New York, Maryland Med. Jour., 1891-92, p. 463.

28. Brena, T.: Rough Notes on the Etiology of Typhus Fever, Am. Pub. Health Assn., 1898, p. 206.

29. Mahon, R. B.: The Causes and Management of Outbreaks of Typhus Fever in Rural Districts, Jour. State Med., 1899, p. 394.

Before Matignon[30] came to Pekin, there was no typhus fever but a *fièvre de Pekin* which this author recognized as the European typhus fever. The predominating symptom in these cases was again intense headache.

How mild some of these cases may be is shown by a case of another author,[31] who writes:

> There are even ambulatory cases: in spite of high fever, prostration and cephalalgia, the patient can walk. A Chinese, sick for five days, with a temperature of 40.4 C. (104.7 F.) came on foot from a distance to the French legation to ask for a consultation, and was able to walk to the hospital, a distance of about 2.5 kilometers, or about a mile and a half.

From this case it may be seen how difficult it may be under certain circumstances to make a correct diagnosis in sporadic cases.

I now come to the discussion of the Manchurian type of typhus.

S. S. Botkin observed in the Far East a peculiar typhus with eruption, but without mortality or contagiousness. The pathological anatomy could not be studied, because there was no mortality. When the author read a paper describing his investigations, he found that the affection was known to the local physicians, who called it Manchurian typhus. During a discussion before a St. Petersburg medical society, a physician, Dr. Popoff, stated that he had likewise seen such cases in Warsaw, Poland.

S. S. Simnitzky[32] reported two house epidemics of Manchurian typhus fever in 1907 and in 1908. In both instances the lodging-house and prison of Harbin were visited by the disease. The first time five persons were affected, the second time nine. According to this author, the disease has only slight tendency to spread and caused but slight mortality.

B. A. Barikin[33] states in regard to the "so-called Manchurian typhus," that during epidemics of typhoid and paratyphoid there are occasionally cases which in Europe are regarded as typhus, but they are distinguished by slight mortality and slight contagiousness.

Horiuchi[34] succeeded in cultivating from the feces, and in a few cases also from the urine of patients, a well-characterized bacillus which, from its agglutination with the serum of the patient or of others affected with the disease, seemed to him to be the specific pathogenic factor of this affection.

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30. Matignon, J. J.: Le typhus des Européens à Pékin, Jour. de méd. de Bordeaux, 1896, p. 437.

31. Matignon, M.: Le typhus à Pékin, Arch. de méd. et Pharm. mil. 1897, p. 12.

32. Simnitzky, S. S.: Rûsski Vrach, 1907, No. 49.

33. Barikin, B. A.: Russki Vrach, 1909, No. 2, p. 46.

34. Horiuchi, T.: Ueber einen neuen Bacillus als Erreger eines exanthematischen Fiebers in der Mandschurei während des japanische-russischen Krieges, Centralbl. f. Bacteriol., xlvi, 586.

Ricketts and Wilder[35] quote and publish the most recent observations of the contagiousness and transmissibility of typhus fever and of related infections. According to them, Nicolle and his associates have shown that typhus could be transmitted to the chimpanzee by the injection of the blood of human patients and then the disease could be transferred from the chimpanzee to the macacus monkey. In the latter species it could be propagated by the ordinary body lice.

Spotted fever is a disease which, to judge by the descriptions, has a great deal in common with typhus fever. This disease has been specially studied by Ricketts and Wilder, who have shown that it is not contagious at all, being transmitted by the bites of certain species of ticks, so that the presence or absence of this variety of insect determines the state of the disease in any locality. So far as Mexican typhus, or tabardillo, is concerned, these authors are of the opinion that lice are probably the means of transmission of the disease. The flea is excluded from serious consideration because the season of the greatest prevalence of this insect does not coincide with the prevalence of typhus, while individual cases observed by them seem to absolve the bedbug from all blame in the matter.

The words of these authors[36] in reference to typhus fever deserve to be quoted literally, as they are very much in accord with the views defended in this paper:

> It is a peculiar fact that the conception of contagiousness has adhered to typhus up to, and including, the present time. Yet, in view of the facts that typhus, when endemic in the city, remains rather strictly segregated in the poor quarters, and that more or less intimate contact is required for transmission, it is manifest that contagiousness, if present at all, must be of peculiar character and of low grade. Typhus has never overwhelmed a whole city as small-pox did again and again in former times. In recent years, however, belief in the theory of insect transmission of typhus has extended widely, as affording a better explanation of the epidemiological features of the disease.

If Nicolle's results in transmitting typhus by means of lice be provisionally accepted, they throw additional light on the apparent immunity of Brill's ward patients to the infection from neighbors suffering with the disease he has described. It is well known that lice rarely travel from bed to bed as fleas and bedbugs do; more intimate contact than mere proximity is required for their migration and, with it, for the transmission of any infection they may carry. It may be accepted that the wards of the Mount Sinai Hospital show no exceptions to these observations.

I cannot enter here on the details of the clinical picture, but from descriptions the Manchurian type of typhus seems quite similar to Brill's and to the mild and medium cases which I have seen in European Russia.

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35. Ricketts and Wilder: The Typhus Fever of Mexico (Tabardillo), Jour. Am. Med. Assn., 1910, lv, 463.

36. Ricketts and Wilder: The Relation of Typhus Fever (Tabardillo) to Rocky Mountain Spotted Fever, THE ARCHIVES INT. MED., 1910, v, 361.

The various observations, both personal and taken from recent medical literature gathered in this paper, show that the symptom-complex described by Brill is identical with that of the mild and moderately severe cases of typhus fever. In other words, his cases are not a new "clinical entity" but examples of an old though nowadays but imperfectly known disease. Typhus contagium, too, may always exist in a community yet not necessarily lead to an epidemic at any definite time, for innumerable local conditions may be the determining factors in the development of an epidemic. Who knows but that the cases "simulating typhus" and reported by Hubbard and Brill are not direct descendants from the cases of the epidemic of 1892?

In any case, mere diminution of mortality and contagiousness should not lead us astray, for it is impossible to estimate the effect of modern hygienic and sanitary precautions on the character of such a disease of filth, hunger and poverty as typhus fever. Moreover, fatal cases have been observed by Brill in patients treated under the best conditions, that is, in the hospitals, and the mortality of from 6 to 9 per cent. observed by me in the general practice in a small Russian town does not then appear so greatly different. The fact that mostly Hebrews were affected among Brill's cases must also be remembered; the statistics I have mentioned in discussing typhus among the Arabs shows how important are the racial peculiarities in this connection.

Of course, time alone will decide the question of properly classifying the symptom-complex so ably observed and described by Brill. In the meantime, however, it does not seem to me to be part of wisdom to retain his nomenclature of a "disease of unknown origin," but rather call it New York typhus, just as the typhus of Pekin and of Manchuria has been named. This would go far in calling the attention of physicians to the clinical picture concerned, and, moreover, not connote something surely rare and unusual. The name "typhus" need cause no panic, as I have tried to show in the preceding pages, for it is no longer equivalent to the terrifying news, *Hannibal ante portas.* Modern conditions have robbed this scourge of mankind of much of its terror.

CONCLUSIONS

1. Typhus fever occurs sporadically in many regions.

2. Mortality from typhus fever no longer reaches the high figures quoted by old observers of the disease.

3. Typhus is little contagious wherever good ventilation, abundance of light and good hygienic conditions exist.

4. Epidemics of typhus may occur at very infrequent intervals even where the disease is endemic.

5. Brill's symptom-complex is identical with mild and moderately severe cases of typhus fever.

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CORRELATION OF CLINICAL PROGRESS WITH THE RESULTS OF IMMUNOLOGICAL STUDIES IN PULMONARY TUBERCULOSIS *

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One of the most striking features of tuberculosis is its clinical variation. Thus, if one is given a picture of the amount and kind of anatomical involvement, one can form but little estimation of the probable duration of the infection, its past variations or future possibilities; and one frequently finds that, if to this there be added the results of the general clinical inspection and as accurate an anamnesis as it is possible to obtain, the careful observation of some weeks is further necessary before one feels acquainted with the type of case, which even yet may develop unexpected traits. Intuitively, one may feel indefinite indications which may or may not be subsequently verified. Of course these statements are comparative, and like all such in medicine depend to some extent on the clinical experience and judgment brought to bear on the case; but under any circumstances these considerations seem to be distinguishing features of this infection.

These peculiarities help complicate both the diagnosis and prognosis and are chiefly concerned with the resistance of the patient. It is on the type of resistance that I wish to present data. Before attempting this, it seems necessary to consider also the unusual range of tuberculous infections. Roughly, we have the clinically normal case which gives tuberculin reactions; involvement of glands, serous membranes, skin, etc., which apparently remain confined to these structures; the variations of pulmonary tuberculosis; and finally, the typical miliary tuberculosis or tuberculous septicemia.

Now the various immunological procedures that have been meant to aid diagnostic or prognostic values even in pulmonary tuberculosis have been confined to certain distinct types; but in the main, it has been the results obtained with the "normal" that have prevented the general acceptance of the tests in purely clinical work. Usually the tests fail to give 100 per cent. positive results with cases; and they involve the normal as well, so that the general verdict is: Of what use are they in doubtful cases in which they are most needed? It is probably not the procedures that are at fault, but rather our method of application.

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*From the Pathological Department of the National Sanitarium Association.

Agglutination, the precipitin and tuberculin reactions, leukocytic and opsonic estimations share this disadvantage.

If, however, one uses these methods not as an aid to diagnosis or prognosis at first, but rather to demonstrate evidences of the biological state — as one would use the various methods of a physical examination of the chest to depict the anatomical involvement — the results assume not only an interesting but a valuable force. Obviously, the biological state, if demonstrated and understood in its entirety, must precede rather than accompany the anatomical involvement. The clinical responses are due to the biological variations.

As a means of showing these biological variations I shall present certain procedures,[1] which will frequently be referred to for greater detail, all of which have been carried out on fairly large numbers of cases, and further attempt to correlate the results of these with certain clinical recognitions.

I. TUBERCULIN REACTION

1. A positive result means only that the subject has been exposed to tuberculous infection and has reacted biologically. This specific state lasts for a varying period in both clinically normal and tuberculous subjects. Certain cases of pulmonary tuberculosis after years of infection may still show this markedly. This state may be taken as evidence of one part of the mechanism of resistance, and by itself can demonstrate only approximately the presence or absence of those bodies concerned in its production.

2. A negative result presents three considerations:

   A. No exposure.

   B. Loss of sensitiveness.

   C. Anergy — the development of a condition refractory to tuberculin (comparable to the antianaphylactic condition in anaphylaxis).

It is not always possible to distinguish, in cases giving slight reactions, between the second and third types. When loss of sensitiveness is taking place, it represents a partial victory by the infection against the host, and the accompanying clinical correlation probably depends on the extent to which the particular patient is utilizing the bodies concerned in the reaction for maintenance of life. This can sometimes be approximately gauged by the estimation of other resistance products. The refractory condition does not seem to represent an infection victory but rather the reverse. It is not only convenient to take this tentative hypothesis, but apparently true clinically.

II. COMPLEMENT DEVIATION

Complement deviation must be considered in both a specific and non-specific light. As the former it is the true Bordet-Gengou phenomenon,

1. These have been published in the Jour. Med. Research, xxiv, No. 1.

as the latter it is exemplified by the Wassermann reaction for syphilis. Probably the results obtained in tuberculosis are influenced by both factors, but accepting a certain type[2] of positive reaction as evidence of tuberculous sensitizers, the following statements can be made:

1. It is not obtained in the clinically normal giving tuberculin reactions.

2. Its presence in the tuberculous is usually found among the more unfavorable type.

These facts as well as other considerations suggest two theoretical conceptions: either tuberculous sensitizers are not produced by favorable cases and "normals" showing tuberculin sensitiveness, or they are produced, though their presence is in some way masked.

III. INHIBITIVE REACTION

In attempting to solve this problem it became possible to show with the serums of certain favorable cases not giving evidence of sensitizers, an antigen-serum combination or effect that is non-attractive for complement. Consequently, with the technic of the deviation test complete hemolyses results.[3] This reaction capacity can conveniently be termed inhibitive. For purposes of expression only, it is convenient sometimes to speak of such inhibitive-reacting serums as containing inhibitin. Further, if such antigen-serum mixtures are again treated by a sensitizer serum, the end-result of complete or no hemolyses can be shown to depend on the relative strength of the opposing serums.

IV. INDIFFERENT REACTION[3]

From the technic employed, a third type of serum becomes evident in that there is no evidence of either sensitizers or inhibitin. This can conveniently, for these purposes, be termed "indifferent" (or Class III).

From the results of the immunological procedures so far dealt with, one may tabulate the following demonstrations:

1. By tuberculin reaction.
   - A. Allergy or marked sensitiveness (host defense).
   - B. Loss of sensitiveness (infection victory).
   - C. Anergy or refractoriness (host defense).
2. By complement deviation and its modification.
   - A. Complement fixation — tuberculous sensitizer (Class II).

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2. This has been to some extent discussed (Jour. Med. Research, see Note 1) and will be dealt with again in a later publication.

3. As outlined in the previous paper the inhibitive serum effect becomes differentially demonstrated when employed with strengths of antigen, which of themselves non-specifically fix complement. With true antigenic strength, no more is demonstrated than that these serums do not fix complement. For practically all this work an alcohol-ether extract of the bacillus has been used as antigen.

B. Inhibitive reaction — inhibitin (Class I).
C. Indifferent reaction — (Class III).

1. Correlation of Certain Clinical Considerations with Tuberculin Reaction Results

A. Onset.—Typically this is acute with cases showing marked sensitiveness, a history of which has never been obtained in my comparatively few definite instances of refractoriness.

B. Duration and Involvement.—With increase of involvement usually sensitiveness tends to disappear, and as a general rule with length of duration also. There are, however, instances of marked sensitiveness being maintained throughout a long period (three to five years) of infection with extensive involvement. In a few instances, considerable variations of sensitiveness have apparently obtained throughout the course of the infection.

C. Variation.—When this is marked and acute with regard both to clinical response and anatomical involvement, it has in my observation been confined to cases showing marked sensitiveness. The reverse also obtains, viz., definitely refractory cases do not show marked or acute clinical variations of response and anatomical involvement.

D. General Prognostic Values.—Loss of sensitiveness is likely to be followed by retrogression, as has been outlined already in the theoretical remarks on the tuberculin reaction. Not all cases showing marked sensitiveness or refractoriness, however, can be classed as favorable without further discrimination by the results of the following reactions. It would seem that the results of this additional biological discrimination harmonize with certain opposing observations on the prognostic value of the different tuberculin reactions.

2. Correlation of Certain Clinical Considerations with the Reaction of Fixation (Tuberculous Sensitizers)

A. General Tendency.—Usually they are cases of doubtful tendency and extremely liable to acute and sudden clinical outbreaks with often corresponding alterations in the anatomical involvement. As far as can be judged, all show tuberculin sensitiveness; usually this is marked.

B. Temperature.—This is frequently pronounced in the outbreaks. From considerable opportunity for observation where this has not been checked by continued, even absolute, rest in bed and by contrast with reverse treatment, it would seem that in these cases a repeated record of even 99 F. should be checked by rest in bed, and if this is not effectual the rest should be made absolute.

C. Variations in Progress.—One case (864[1]) has come under observation in which the fever and retrogression of the case eventually became beyond control, resulting in early death. This patient with considerable irregularity in her fever chart, with frequent records of 100 F. and more or less often 101 F. and 102 F., alternated at first from periods of some rest in bed to the activity of being up and about. Biological observations were repeatedly made, and latterly as the severity of the clinical response became more marked, it appeared that the sensitizer content increased, with concomitant loss of thermolabile quantities in the serum. This is the only case beginning with slight involvement that has run a rapidly fatal course when these routine biological procedures were performed; but from certain other closely related immunological tests it seems fair to infer that these conditions were present in two other cases with similar histories. This conclusion is strengthened by several incomplete observations such as the following: Case 1761 was referred to the laboratory as an instance of more or less frequent onsets of temperature; had been classed as Turban Stage I in April and on the second subsequent examination in October as Turban Stage II with increased activity. Three tests at different times showed the presence of tuberculous sensitizers.

Since the earlier observations made on cases, many of which have given very distinct indications toward early and fatal terminations, it has become evident that favorable local progress may occur in these cases; but in every instance in which this has occurred, rest has carefully been enforced. In this connection the following case may be reported.

CASE 1052 has shown remarkable power to "clear" (spring 1909) without retraction, the anatomical condition from a Turban Stage III of marked activity of at least a year's duration. About a year later, after a prolonged setback during which time this serum content was present, striking retraction of the chest resulted. The reaction was last obtained early in June, 1910, since then the temperature has gradually subsided and the general well-being has gradually improved. Since August, 1910, the charts have shown a practically afebrile condition. At this date, the chest for the first time showed some evidence of fibrosis, although unfortunately it was impossible to carry out the biological tests. Later, in November, the retraction had become marked with improvement in the physical signs, and for the first time there was no evidence of the sensitizer content, although the tuberculin sensitiveness was as marked as at the first estimation. The condition of well-being and lack of clinical response at both favorable periods are indistinguishable; the type of local improvement and the serum reactions alone are different.

Two other cases which illustrate variations that have been fully followed are as follows:

CASE 1169.—Aug. 10, 1910. A man aged 22. General appearance at present not good.

Weights.—Admission, 158; normal, 170; 145 at 15 years; present 174.

History.—Diagnosis was made May, 1909, when the patient entered a hospital for bronchitis; he had not felt well for a greater part of the year, particularly in January when he stayed in bed with fever without medical attention. After

diagnosis, the patient, on leaving the hospital, resumed work and felt well till August, at which time he was taken quite suddenly with fever. With more or less rest he improved, began work in October and continued till January, 1910, when a second breakdown occurred. He entered a sanatorium January, 1910, as Turban Stage II, moderately advanced. He was discharged Feb. 3, 1911. The institutional charts show variations but no maintained improvement. Apparently, there was an increasing number of slight outbreaks from June till November. From November 7 till December 6 the temperature record shows an irregular curve with several registers over 100 F., during which time the patient might be said to be on more or less rest in bed. From December 7 till January 5 there is no register above or much below 98 F. On January 5 there is a fairly distinct curve reaching 101 F., which acuteness subsided January 16. January 13, absolute rest was enforced.

The following biological data have been obtained:

Nov. 3, 1910: Class 2 (Tuberculous sensitizers).

Nov. 16, 1910: Class 2 (Tuberculous sensitizers).

Jan. 3, 1911: Class 3 (indifferent reaction).

Jan. 14, 1911: Class 2 (tuberculous sensitizers).

Feb. 3, 1911: Class 2 (tuberculous sensitizers).

From the biological work it seems impossible to represent graphically these correlations in their exact quantities—if such do exist—but the accompanying diagram may serve approximately to illustrate.

CASE 1371.—March 11, 1910, a man aged 19. General appearance fairly good.

Weights.—Admission 121, at time of investigation, 134, normal (approx.), 126.

History.—Diagnosis made Aug. 3, 1910. The patient, though not confined, had been under treatment for pleurisy since April, and frequently examined for pulmonary involvement; for about a month previous to diagnosis of pleurisy he had not felt well, having had indefinite chest pains and some shortness of breath.

Institutional Charts.—September, Turban Stage II, moderately advanced—right-sided lesion with very distinct percussion and auscultatory signs. By December 31, the charts are marked clear with the exception of slight signs over the posterior apex and slightly more marked conditions about the front apex of the lower lobe. The laboratory chart of Nov. 22, 1910, shows slight involvement on the left side as well; a further anatomical interpretation was made of marked pleural involvement.

Biological Data.—November 3: Von Pirquet 50 per cent. O. T. (10 c.mm.) color 30 x 30 mm. from second to fourth day with subsequently gradual subsidence; swelling corresponds and is soft in character.

November 3: Class 2, i. e. tuberculous sensitizer serum.

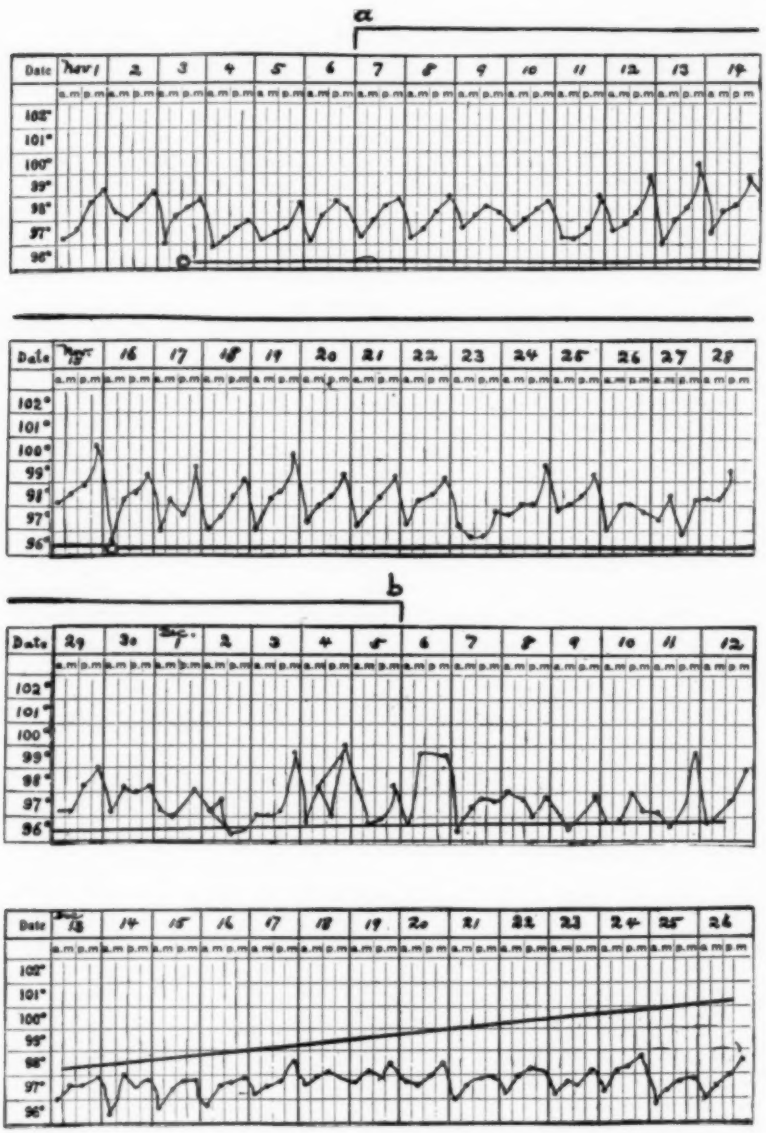
December 16: Class 2, tuberculous sensitizer serum.

Apparently, steady local as well as general improvement took place in the presence of tuberculous sensitizers.

Treatment in Particular.—Tuberculin and rest for a temperature of 99 F. which has occurred on three occasions.

This patient, in contrast to the preceding, made continued progress and the sensitizer content eventually disappeared.

D. General Considerations.—These cases, when persistently showing retrogression, have given with increase of the sensitizer strength a loss of certain thermolabile constituents. If we base our conclusions chiefly on earlier observations, these cases are extremely liable to develop unfavorable progress, unless rest is carefully enforced. With this régime, instances have occurred of stationary and more or less favorable local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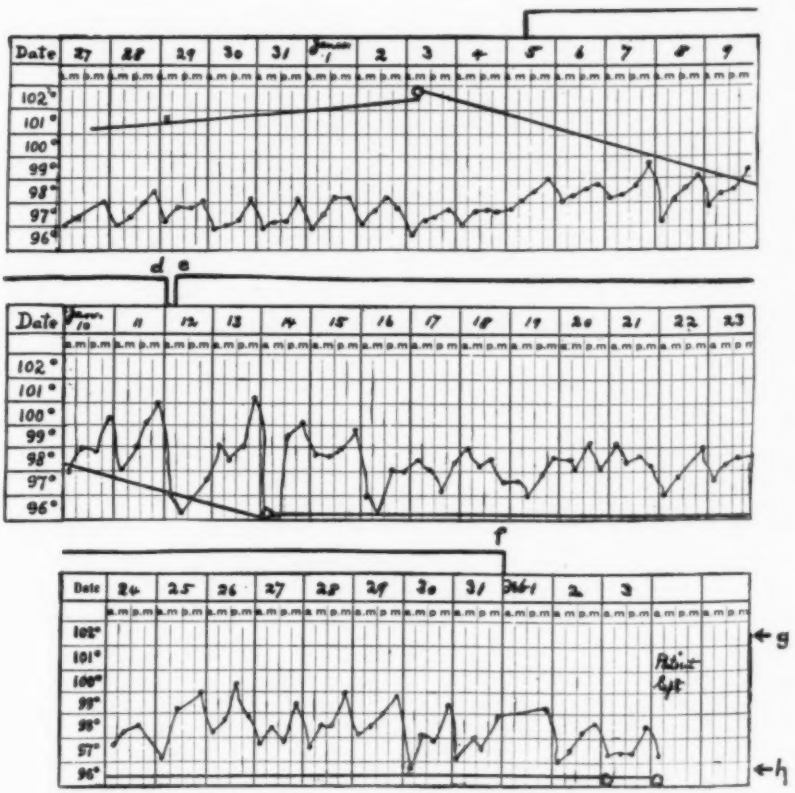


Fig. 1.—Chart of Case 1160. Line with nodes indicates temperature. Heavy straight line indicates serum reaction curve. The circle (o) indicates dates of serum reaction. From *a* to *b*: more or less incomplete rest. From *c* to *d*: rest. From *e* to *f*: absolute rest attempted—not quite satisfactorily obtained. The mark *g* indicates indifferent serum reaction; *h* indicates tuberculous sensitizers.

changes, under which circumstances eventually the sensitizer serum content has with temporary exceptions disappeared after, as far as can be judged, the subsidence of the clinical responses.

3. Correlation of Clinical Considerations with the Inhibitive Reaction

A. Early Cases.—Patients with slight involvement (early cases) in good general condition, nearly, if not always, have given this reaction. The possible exception is noted chiefly because of the doubtful nature of the diagnosis in certain cases that might be included in this class.

B. Normals.—Clinical normals giving tuberculin reactions have so far all shown some inhibitive reaction; while (few observations made)

favorably progressing cases of glandular and serous membrane involvement have given this in full.

C. Involvement.—Quite frequently cases are found with extensive anatomical involvement and signs even of fairly marked activity; in these cases considerable work may show no unfavorable effect. In all these the inhibitive reaction has been present to some extent, though not usually to the full extent.

D. Temperature.—This correlation has been obtained in two somewhat different fashions. In the first method, observations have been made to a considerable extent on about twenty-five patients in bed, but for various reasons these observations have not been systematically repeated. Among these, some have shown traces of the reaction, a few have shown the complete inhibitive reaction, while the immediate progress has proved doubtful or stationary. In every case (with one exception, in which the test was not made), these doubtful subjects have shown distinct loss of tuberculin sensitiveness. The results were almost entirely obtained among various types of Turban Stage III involvement, in which the work has shown that varying amounts of inhibition may be obtained with considerable clinical response and a bare ability to maintain a stationary local condition. Theoretically, this does not seem at variance with one's conceptions if the reaction is regarded as a quantitative method, indicating what seems to be the main type of resistance contents. In view of these conditions one feels that each case must be considered by itself in the fullest manner both clinically and biologically. Among these cases with febrile tendencies more than elsewhere, there have seemed to be questions of internal medicine and surgery with their possible bearing on the general welfare of the patient — and also where the involvement is slight, questions of diagnosis. Occasionally, observations have been made regarding the beneficial effect of exercise on certain of these cases hitherto confined; and this is in extreme contrast to my experience with cases showing tuberculous sensitizers. These limitations and indications are somewhat fully exemplified by the following case.

Case 1109.—Aug. 31, 1910, a woman, aged 25. General appearance, slight; temperamental, moderately good.

Weights.—Admission, 117; at time of investigation, 121; normal, 120.

History.—Diagnosis made August, 1910; the patient sought medical advice because of slight cough and marked lethargy which seemed to increase after an attack of measles in May; the symptoms were indefinitely spread over the preceding year. During the two weeks preceding the investigation, and occasionally before, the patient was in bed because of fever.

Institutional Charts.—Aug. 31, 1910 (first examination classed as Turban Stage I): Right apical involvement extending in front to third rib and behind to well below the posterior apex; moderate signs of activity noted. The second examination showed a stationary condition.

Dec. 8, 1910 (third examination): No signs of activity are recorded; impairment of resonance being noted only at both anterior and posterior apices.

The fourth chart, Feb. 22, 1911, shows but slight signs of doubtful character.

Biological Data.—Nov. 6, 1910: V. Pirquet 50 per cent. O. T. (10 c.mm.) maximum color (faint) 30 x 38 mm. on fourth day with somewhat more extensive swelling, soft in character.

Nov. 3, 1910: Class 1—with very slight inhibitive reaction.
Nov. 16, 1910: Class 1—some inhibitive reaction.
Dec. 17, 1910: Class 1a—full inhibitive reaction.

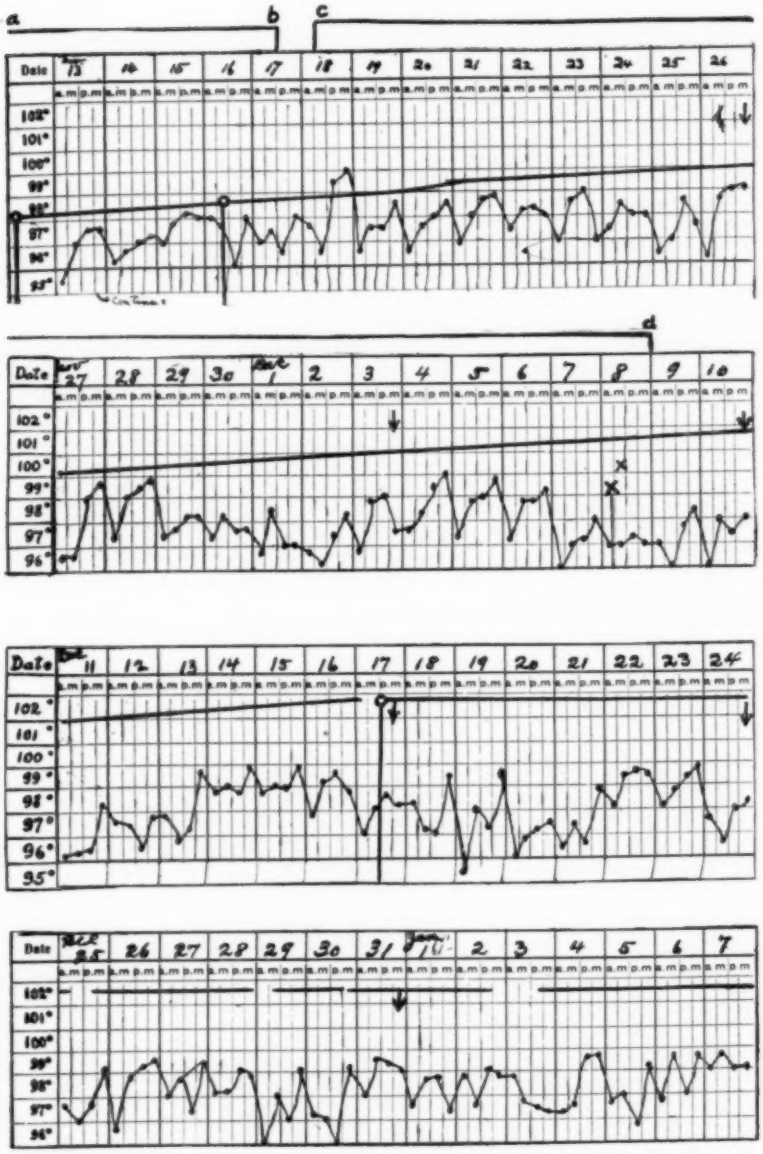
In this instance, the considerations regarding questions of internal medicine have not been definitely settled so that they need not be taken up here, although for evident reasons they have to be considered. Chiefly on account of the biological findings it was requested that this case be kept up in spite of the temperature, and tuberculin was administered. The possibility of the medical complication would not have been considered, had not the biological data been obtained. Beyond the biological evidence the indications pointed toward probable retrogression, until the time of the third examination; all examinations were made by the clinical staff.

The second fashion in which temperature has been observed has been on subjects more or less approximating the type described under Paragraph C of this heading, and in connection with whom for various reasons more systematic checking has been possible. Here, in several instances, after varying periods of temperature (where the inhibitive reaction has remained the same) I have usually been unable to satisfy myself of any definite local change, while later the patients apparently assumed their previous condition of well-being.

E. Variations.—This paragraph can conveniently be introduced by the statement that up till the present there has been no instance of a case giving and maintaining a full inhibitive reaction, marked tuberculin sensitiveness or definite refractoriness that has not progressed very favorably — usually making either an arrest or apparent cure, although this naturally is dependent on the time of observation.

This ability to resolve fairly rapidly the anatomical involvement — as judged by our physical methods — in contrast to those cases in which this does not obtain, although the patient may make slow and slight local improvement or good progress in the general well-being, seems very definitely associated with these two biological conditions. That other biological conditions may sometimes approximate this clinical result is shown in certain of the histories under Heading 2; and as well in certain subjects about whom it is not possible as yet to arrange the scattered immunological data.

Probably owing to the fact that very few patients reach my department until some time after arrival, there have been only a few instances of increase in the inhibitive serum content. In one of these, particularly, the accompanying clinical improvement has remained in marked fashion (Case 1107).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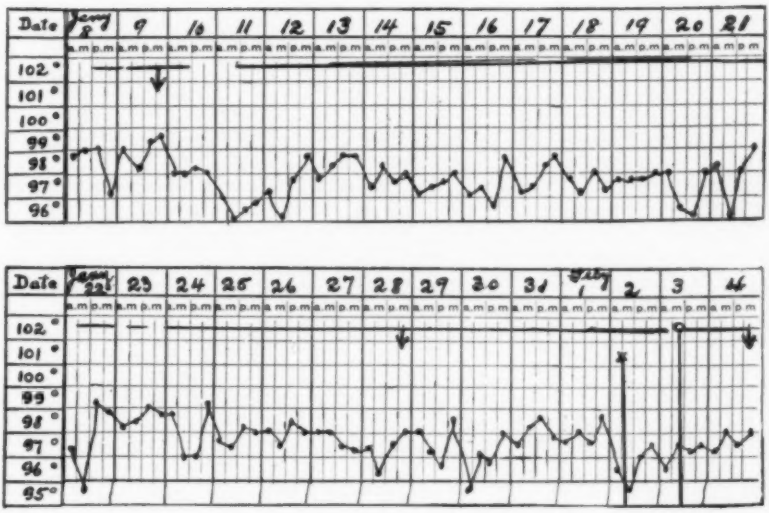

Fig. 2.—Chart of Case 1109. Line with nodes indicates temperature. Heavy line indicates serum reaction curve (when at the top, inhibitive reaction; when at the bottom, indifferent reaction). The circle (o) indicates dates of serum reaction (beginning with third reaction); *x* indicates third and fourth physical examinations, respectively. Knowledge of anatomical progress remained in *status quo* (Turban Stage I, with activity) until third examination on Dec. 8, again in February showing the continued improvement. As far as determinable, the rise in the inhibition content preceded the favorable local changes.

On the other hand, there have been many instances of loss of the inhibitive reaction followed or accompanied by slight increase of local involvement, or suggestive specific clinical response, or both, when often at the time of the biological observations this might not have otherwise been observed. Particularly lately, as the number of patients and the time since their reaction observation increase, have these correlations been accumulating. This has been so definite and is of such importance that it seems worth while to outline instances dealing with different amounts of involvement and type.

CASE 312.—A man, aged 24. General appearance splendid.

History.—Diagnosis made January, 1910; the patient had had a small hemorrhage while playing sport in December, 1909; later the *B. tuberculosis* was found in the sputum; there was a history of some lassitude and slight cold during December only.

Institutional Charts.—January, 1910, slight right apical lesion with involvement of the posterior apex (classed Turban Stage I incipient).

By June 16, the charts are marked clear with the exception of very slight evidences at the posterior apex. During August and September, the posterior apex is marked clear, although again some slight evidences are marked anteriorly. These two charts seem to be the best. From this time onward, varia-

tions have increased so that the December and January (1911) charts show an anterior involvement extending slightly into the middle lobe and record showers of râles on coughing.

Biological Data.—Jan. 26, 1910: Von Pirquet 50 per cent. old tuberculin (10 c.mm.) maximum color 60 x 50 mm. on the third day with indurative swelling 30 x 25 mm.; some lymphangitis.

June 12, 1910: Class 1. The full inhibitive reaction had been obtained many times previous to this date, as this serum had been used considerably in advancing the theoretical parts of the work. This was the last date, on which this full inhibitive reaction was obtained, although subsequent work on June 14 suggested that it was not so strong or efficient as previously. During August work with a new extract which proved unreliable gave certain indications that the reaction was less marked. However, the conditions at the time of the last reactions were such that no positive value can now be attached to these indications.

Nov. 3, 1910: Class 3 (indifferent reaction).

Nov. 17, 1910: Class 3 (indifferent reaction with the faintest suggestion of inhibition).

Dec. 16, 1910: Class 1a (full inhibitive reaction).

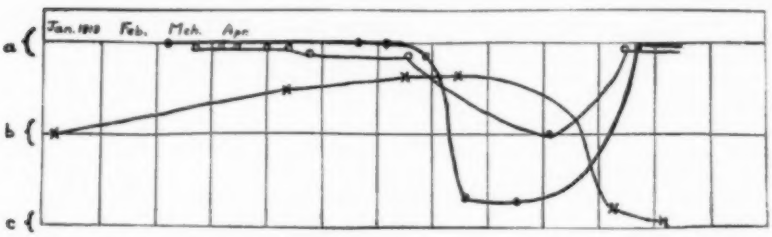

Fig. 3.—Line with nodes indicates subjective indications; line with circle (o) indicates serum reaction; line with crosses (x) anatomical involvement. Chart of Case 312. (a) Top: full inhibitive reaction; no evidence of anatomical involvement; subjective indications, normal; (b) middle: indifferent reaction (Class III), Turban Stage I, suggestion; (c) bottom: *tuberculous* sensitizers (Class II); Turban Stage II; definite.

During the latter part of September and October and part of November, this patient gave rather indefinite symptomatic complaints that might have been explained by a saturation with sanatorium life. At this time the patient took a considerable number of leaves of absence. During December the general condition improved. It should be stated here that the physical charts[4] were made without knowledge of the biological findings until after November 3, and that the charts exhibited their fullest involvement only some time after the biological variations and at a time when these latter had returned to their former favorable condition. If the indefinite general symptoms can be accepted, the biological relations accompanied them (unfortunately repeated cutaneous tests were not feasible) and definitely foreshadowed the anatomical involvement as inferred from the physical examination. These remarks may be graphically charted in an approximate fashion (Fig. 3).

Case 1372.—M., a man, aged 19. General appearance, very good.

Weights.—Admission, 149; at time of investigation, 155; normal, 146.

4. This remark applies to most, if not all, charts quoted as institutional. The observations, clinical histories, etc., have been made by the pathological department. It seemed, however, that for this paper the use of the physical charts of the clinical staff would show an unbiased parallel.

History.—Diagnosis made August, 1910; the patient had passed through treatment by three physicians for lethargy and cold with cough since March; these symptoms were particularly noticeable since April; the highest temperature recorded was 99 F. Family history marked.

Institutional Charts.—November 5: Turban Stage I incipient, slight left apical involvement to third rib in front and the posterior apex behind.

Dec. 9, 1910: There is an impression of possibly less involvement.

Jan. 17, 1911: Bilateral involvement both anteriorly and posteriorly without much evidence, however, of activity, might be classed as Turban Stage II.

The results of the laboratory charts made in November and January correspond, though less noticeably, to this variation; further, certain anatomical interpretations made in the first were obscured or altered in the second.

Biological Data.—Nov. 16, 1910: Class 1a (full inhibitive reaction).

Jan. 14, 1911: Class 3 (indifferent reaction with the faintest suggestion of former Class 1 phenomenon).

Feb. 3, 1911: Class 3.

The first chart shows variation occurring in January. There was nothing in the patient's general condition to suggest that a change of progress was taking place, which is perhaps the fairest fashion to interpret the anatomical findings under the routine circumstances. The case has been afebrile and has shown continued improvement in general well-being.

CASE 1105.—Sept. 3, 1910: A man aged 20. General appearance—good; well nourished.

History.—Diagnosis made November, 1909 (after a two weeks' illness of acute onset with temperature of 103 F.); the certainty being confirmed by the presence of the *B. tuberculosis;* the year previous to diagnosis suggestive but ill-defined symptoms.

Institutional Charts.—December, 1909: Bilateral involvement of moderate activity classed as Turban Stage II, moderately advanced. By August the charts showed very distinct improvement. From this date till the present, slight variations are shown which practically leave them in *statu quo* in contrast to the previous improvement.

Biological Data.—March 9, 1910: Von Pirquet 50 per cent. old tuberculin (10 c.mm.) color 30 x 20 mm. with indurated swelling.

March 9, 1910: Conjunctival 5 per cent. old tuberculin (10 c.mm.) + +.

April 19, 1910: Class 1a (full inhibitive reaction).

June 12, 1910: Class 1 (partial inhibitive reaction).

Nov. 3, 1910: Class 3 (indifferent reaction).

With the inhibitive reaction there was always some deflection of complement with antigenic strengths, a result noticed in later work with serums, which often subsequently lost the reaction content. Certain symptomatic evidence corresponds to the lack of improvement, and very definitely is this evident with the temperature records. These from March 16 till August 3 show no register beyond 98.4 F. From this time on, there are many but irregular variations outside the normal range.

CASE 302.—Clinical normal. April 16, 1910: (Third cutaneous test on left forearm) Von Pirquet 50 per cent. O. T. 10 c.mm.

April 17: Color 10 by 12 mm.—no swelling.

April 18: Color 15 by 18 mm.—no swelling.

April 19: Color 16 by 20 mm. with equal swelling that is clear cut and indurative.

April 20: Color 18 by 20 mm. with equal swelling that is clear cut.

April 21: Gradual subsidence.

April 16: Conjunctival 5 per cent. O. T. (10 c.mm.) negative.

October 7, 1910: Von Pirquet 50 per cent. O. T. (10 c.mm.) on right forearm.

October 8: Color 20 by 18 mm.—no swelling.

October 9: Color 20 by 20 mm.—no swelling.

October 10: Color (patchy) 20 by 20 mm.—no swelling.

October 11: Gradual subsidence. The reaction was not affected by exercise and the color throughout was very easily pressed out.

Up till the following data, all clinical normals giving tuberculin reactions had shown repeatedly "some" inhibitive reaction with one doubtful instance.

Nov. 3, 1910: Class 3 (indifferent reaction).

November 16: Class 3 (very slight evidence of inhibitive reaction).

Jan. 3, 1911: Class 1a (full inhibitive reaction).

February 3: Class 1a (full inhibitive reaction).

This is the only example found of a clinical normal giving a full inhibitive reaction. The subject has been fairly intimately exposed to tuberculosis, but particularly so in August, 1910.

This serum has been used in the technic many times prior to August and with one possible exception, when it was old, has always shown some evidence of inhibition. Unfortunately, it happened that no reaction was made during September and October; the last two being on July 20 and 23. Further, the fourth cutaneous test is distinctly different in type and onset from the three previous, which have been more fully considered in the first publication. It seems impossible to ignore, at the least, a diagnosis of biological or anatomical tuberculosis.

As the reliability of these observations has increased, every endeavor has been made to check the life of the patient when a change in the serum reaction occurs. From this one hopes to prove a distinct indication regarding the general handling of cases. However, as can be seen from the remarks under Paragraph C and from theoretical considerations, an unfavorable turn in an inhibitive reacting case may not always be preceded or accompanied by a loss of that serum content. While it is impossible to be certain that this has or has not occurred to some extent in the cases under my observation, no evidence of such has been noticed. On the present theoretical grounds, a loss of tuberculin sensitiveness should accompany this particular retrograde tendency.

4. *Cases Showing the Indifferent (Class 3) Serum Reaction*

This reaction has been found originally and confirmed in (a) definitely moribund cases and (b) others in which the main distinction seems to lie in their slightly plus and minus ability for slow local improvement with varied clinical response. It has been followed in patients who have shown a loss of tuberculous sensitizers and inhibition, and, as far as chronologically ascertainable, may be associated in the former with local and general subsidence, or even improvement, while in the latter with unfavorable conditions both objectively and subjectively. Further, these relations obtain with all varieties of tuberculin type reactions, so that the possible biological states seem confusing. It is on contrast cases of this type, however, that one hopes to show immunological differences that

may be here marked, and which may play an unusual and effective rôle in those cases.

As a result, one feels that pulmonary tuberculosis by itself presents three chief considerations for complete conception:

1. The biological relations (or involvements) of host and infection.
2. Anatomical involvement.
3. Clinical response.

These might be correlated as follows: The judgment of a case depends on one's conception of the biological interactions between host and the infecting tubercle, in consideration of the type, amount and duration of the anatomical involvement, and the resulting clinical response direct or indirect. One feels that all must be considered if one is to escape with the minimum of error in diagnosis, prognosis or treatment. The biological states can but roughly and approximately be estimated, as is also frequently true of the type and amount of anatomical involvement by our physical methods.

One feels that this is an attempt to interpret broadly biological or immunological data into clinical correlation without the almost essential qualification of presenting a critical clinical conception of many cases, and also submitting chronologically the laboratory end-results to a severe comparison with the details of the clinical history and charts. With the majority of cases of tuberculosis it seems necessary to present with their varying fluctuations, during long-drawn-out periods of time, many apparently small irregularities of clinical response and temperament, as well as the graver evidences of the infection, before one feels that the picture is sufficiently detailed. For this reason, only what seem to be the most important and clearest-cut examples have been given. These have been in the greater number of classifications repeatedly observed with slight variations. Clinical manifestations and anatomical involvement for correlation purposes can hardly be dealt with under simple classifications, nor can the biological data be summed up as positive or negative tests. These difficulties have underlain the presentation of the comparisons. The procedures began March, 1910, and up to October had been carried out on sixty-six cases to a greater or less extent, as the more experimental part of the work allowed their clinical application. Since then there have been eighty-four cases under as constant observation as the circumstances of the situation allowed, and the clinical variations in each case demanded. In this way, the serums from nearly all had been tested under many varying circumstances. As serums whose characteristics were determined have been used to further certain theoretical conceptions, frequent checks have been made on the same serum.

The clinical applications have proved to be valuable, and, as they exist, the following considerations seem to be outstanding. With many cases

the occurrence of tuberculous sensitizers is significant, as this condition is in the majority of cases associated with clinical reverses and often acute setbacks with high temperature. Subsidence of the clinical response in a few cases sufficiently closely investigated has been followed by a disappearance of this serum content. Unusual opportunity for observation has demonstrated the great benefit of restricting cases of this type to rest in bed on the slightest appearance of fever; absolute rest being enforced and maintained if the temperature does not respond. The impression is very distinct that rest may be judiciously advised in many cases of this type even when there are no febrile disturbances.

Under favorable circumstances it has been possible to foreshadow both the favorable and unfavorable progress of a case by the come and go of the inhibitive reaction. In certain instances a disappearance of the inhibitive reaction has revealed not more than a stationary condition, in contrast to a previously favorable progress, or to a condition which one had previously conceived in a favorable light. These correlations have been most acutely marked in the early cases of slight involvement. This is proving of value in checking the life of arrested or improved cases in patients on their return to work.

Other aspects of tuberculosis seem to be affected by a consideration of these biological data, such as the administration of tuberculin and the selection of cases possibly suitable for other vaccine therapy; but I have attempted to present what seemed the most important, and have further confined myself to the results of those procedures relating to the humoral side of immunity. Certain possibilities relating to the cellular side are at present under investigation and promise results. One feels constrained to draw attention to this because the purely experimental side of immunity is passing into the hands of the chemical pathologist and physiologist, while the possibilities of the present knowledge are not being applied clinically. Neuberger in speaking of Hippocratic medicine writes: "It is the conception of the medical vocation and the method of medical thought and action, true now as then, that distinguished that period." Would not advancement be materially aided if we regarded the application of immunology as a necessity for the treatment of the patient rather than a method of research?

THE INCOAGULABLE NITROGEN OF PUNCTURE FLUIDS, WITH SPECIAL REFERENCE TO CANCER

A PRELIMINARY NOTE *

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ST. LOUIS

To determine whether a collection of fluid in a serous cavity is of malignant origin is often a matter of considerable difficulty. The specific gravity and albumin content are of little or no value. The usual bloody nature of the fluid is not diagnostic. The only reliable means of detecting a malignant neoplasm from a study of puncture fluids alone has been the finding of mitotic cells — very rarely of tissue fragments — in the stained sediment, and such cells are often lacking.

In view of the demonstration of a proteolytic enzyme or enzymes in carcinomata and sarcomata, it occurred to me that the ferment, if secreted into a serous fluid, might disclose its presence by an increase in the quantity of incoagulable nitrogen. With this idea, the present study was undertaken.

That malignant tumors contain one or more proteolytic enzymes was first suspected by F. Müller.[1] That his surmise was correct has been demonstrated by the work of his pupils, notably Emerson,[2] Fischer[3, 4] and Neubauer,[4] and by others. Petry[5] demonstrated that autolysis occurs in carcinomata, a fact which was confirmed by Neuberg[6] and by other observers. Buxton and Shaffer[7] proved the existence of a proteolytic ferment in cancers, the softer, more cellular tumors usually possessing it in greater abundance. Recently, Neubauer and Fischer[4] and Abderhalden

*From the Clinical Laboratory, The Johns Hopkins University and Hospital.

1. Müller, F.: Stoffwechseluntersuchungen bei Krebskranken, Ztschr. f. klin. Med., 1889, xvi, 496.

2. Emerson, C. P.: Der Einfluss des Carcinoms auf die gastrischen Verdauungsvorgänge, Deutsch. Arch. f. klin. Med., 1902, lxxii, 415.

3. Fischer, H.: Zur Kenntnis des carcinomatösen Mageninhalts, Deutsch. Arch. f. klin. Med., 1908, xciii, 98.

4. Neubauer, O., and Fischer, H.: Ueber das Vorkommen eines peptidspaltenden Fermentes in carcinomatösen Mageninhalt und seine diagnostische bedeutung. Deutsch. Arch. f. klin. Med., 1909, xcvii, 499.

5. Petry, E.: Ein Beitr. zur Chemie maligner Geschwülste, Beitr. z. chem. Phys. u. Path., 1902, ii, 94.

6. Neuberg, C.: Chemisches zur Karzinomfrage; Ueber anormale fermentative Vorgänge beim Krebs, Berl. klin. Wchnschr., 1905, xlii, 118.

7. Buxton, B. H., and Shaffer, P.: Enzymes in Tumors, Jour. Med. Research, 1905, xiii, 543.

and his co-workers[8] have shown that malignant growths contain an enzyme capable of splitting certain polypeptids into their constituent amino-acids. This has led to the introduction by the first-named authors of the glycyltryptophan test for the diagnosis of cancer of the stomach. With the demonstration, then, of a proteolytic enzyme in malignant neoplasms and of the secretion of the ferment into the stomach contents in gastric carcinoma, it is readily conceivable that primary or metastatic growths affecting the serous surfaces might secrete their ferment directly into the serous cavity and, therefore, into fluid occupying the cavity. Following the same line of reasoning, one would also expect to find an absence of the ferment in those fluids resulting merely from the pressure of tumors on important vessels. So that, at the outset, it was anticipated that an increase in the incoagulable nitrogen, if found, would not be met with in all cases.

The method used to remove the coagulable proteins was that of Hohlweg and Meyer,[9] slightly modified. The procedure is as follows: To 10 c.c. of the puncture fluid in a 300 c.c. Erlenmeyer flask one adds a reagent composed of equal parts of 1 per cent. acetic acid and a 5 per cent. solution of monocalcium phosphate until the reaction is acid to litmus but still neutral to Congo red. The limit is rather wide, varying from about 2 to 6 or more cubic centimeters with different fluids. Distilled water is now added to bring the volume to 80 c.c. and then 80 c.c. of saturated sodium chlorid solution are poured into the flask. The mixture is now boiled to precipitate the coagulable proteins and is then filtered through a folded filter directly into a Kjeldahl flask. The Erlenmeyer flask and filter are washed three times with distilled water. A Kjeldahl determination is made on the filtrate. Owing to the quantity of sodium chlorid contained in the latter, a considerable excess of sulphuric acid must be added to convert the sodium chlorid into sodium sulphate and still leave sufficient sulphuric acid for the oxidation. For this purpose about 30 c.c. of concentrated sulphuric acid is enough. Because of the preformed sodium sulphate, it is unnecessary to add potassium sulphate. Otherwise, the usual steps in the Kjeldahl method are carried out. All determinations are made in duplicate or triplicate, after a preliminary test of the filtrate has shown that the proteins are completely removed.

In all, twenty-five fluids have been available for examination up to the present time. The results are given in Table 1, the incoagulable

8. Abderhalden, E., and Rona, P.: Zur Kenntnis der peptolytischen Fermente verschiedenartiger Krebse, Ztschr. f. physiol. Chem., 1909, lx, 415; Abderhalden, E., Koelker, A. H., and Medigreceanu, F.: Zur Kenntnis der peptolytischen Fermente verschiedenartiger Krebse und anderer Tumorarten, Ztschr. f. physiol. Chem., 1909, lxii, 145.

9. Hohlweg, H., and Meyer, H.: Quantitative Untersuchungen über den Reststickstoff des Blutes, Beitr. z. chem. Phys. u. Path., 1908, xi, 381.

TABLE 1.—INCOAGULABLE NITROGEN IN PUNCTURE FLUIDS (AUTHOR'S CASES)

No.	Diagnosis	Incoagulable Nitrogen in gm. per cent.
...	.....	
...	.....	
...	.....	
1.	Hydrothorax, chronic nephritis, arteriosclerosis	0.04585
2.	Ascites, alcoholic cirrhosis of liver	0.0189
3.	Hydrothorax, chronic nephritis, syphilis	0.0665
4.	Ascites, ulcerative endocarditis, arteriosclerosis*	0.03395
5.	Ascites, chronic peritonitis, luetic cirrhosis (?), valvular disease	0.0504
6.	Pleurisy with effusion, pulmonary infarct, chr. nephritis*	0.05425
7.	Pleural effusion, cancer lung and pleura*	0.1162
8.	Case 7, about five weeks later*	0.1120
9.	Hydrothorax, mitral insufficiency, arteriosclerosis	0.03325
10.	Tuberculous peritonitis†	0.0406
11.	Case 1, five weeks later	0.0420
12.	Pleural exudate (?), pulmonary tuberculosis, hypernephroma	0.05145
13.	Pleurisy, lobar pneumonia (empyema developed four days later)	0.0805
14.	Tuberculous peritonitis†	0.0399
15.	Hydrothorax, chronic nephritis, myocarditis*	0.0529
16.	Transudate, pleural (?)	0.03045
17.	Tuberculous peritonitis†	0.0532
18.	Pleurisy with effusion, pulmonary tuberculosis (?)	0.05005
19.	Cancer of stomach, metastases in liver and peritoneum (?)‡	0.1099
20.	Ascites, uterine fibroid (?)	0.0623
21.	Ascites, mitral stenosis and insufficiency, chr. nephritis	0.0413
22.	Hydrocele fluid	0.0532
23.	Cancer of liver, ascites. (No metastases seen on peritoneum)†	0.0371
24.	Hydrothorax, myocarditis, venous thrombosis*	0.0357
25.	Hydrothorax, chronic nephritis, myocarditis	0.0504

*Diagnosis confirmed at autopsy.

†Diagnosis confirmed at operation.

‡Typical case of gastric carcinoma. Tumor at pylorus with stasis; lactic acid, Oppler-Boas bacilli, blood; positive glycyl-tryptophan test; palpable metastases in liver.

nitrogen being expressed in grams per cent. In the literature, no studies of the incoagulable nitrogen in the present connection have been found, but from observations on autolysis of exudates and transudates I have been able to collect a number of records from the publications of Umber,[10] Schütz,[11] Schulz and Müller,[12] Eppinger,[13] Galdi,[14] and Zak[15] (see Tables 2, 3, 4, 5, 6, 7, respectively). The entire material comprises seventy-eight observations on sixty-eight patients. From a study of these values, it is evident that the incoagulable nitrogen of puncture fluids is subject

10. Umber, F.: Ueber autolytische Vorgänge in Exsudaten, München. med. Wchnschr., 1902, xlix, 1169.

11. Schütz, J.: Besteht in Punktionsflüssigkeiten Autolyse? Centralbl. f. inn. Med., 1902, xxiii, 1161.

12. Schulz, O., and Müller, L. R.: Klinische, physiologische und pathologisch-anatomische Untersuchungen an einem Fall von hochgradigem Ascites bei Pfortaderthrombose, Deutsch. Arch. f. klin. Med., 1903, lxxvi, 544.

13. Eppinger, H.: Ueber Autolyse in Punktionsflüssigkeiten, Ztschr. f. Heilk., 1904, xxv (Abt. f. inn. Med.), 378.

14. Galdi, F.: Richerche sull' autolisi degli essudati e dei transudati, Clin. med. ital., 1905, xliv, 65.

15. Zak, E.: Ueber Autolyse in Punktionsflüssigkeiten, Wien. klin. Wchnschr., 1905, xviii, 376.

to considerable variation. (Of the figures given by these writers, only those showing the *initial* amounts of incoagulable nitrogen [i. e., *before autolysis*] are reproduced in Tables 2 to 7.)

I have attempted to divide puncture fluids into three groups according to their content in incoagulable nitrogen, the grouping being provisional and subject to future revision. Group I includes all fluids whose incoagulable nitrogen is 0.0699 gm. per cent. or less, Group II fluids having

TABLE 2.—INCOAGULABLE NITROGEN FROM UMBER'S TABLE*

No.	Diagnosis	Incoagulable Nitrogen in gm. per cent.
1.	Cystic abdominal tumors (autopsy)	0.0515
2.	Tuberculous peritonitis (?)	0.0352

*Umber, F.: München. med. Wchnschr., 1902, xlix, 1169.

TABLE 3.—INCOAGULABLE NITROGEN FROM SCHÜTZ'S TABLE*

No.	Diagnosis	Incoagulable Nitrogen in gm. per cent.
1.	Ascites	0.07245
2.	Ascites	0.02415
3.	Ascites	0.03115
4.	Pleurisy, tuberculous (?)	0.0294
5.	Ascites	0.0303
6.	Ascites	0.02753
7.	Pleural exudate	0.0297

*Schütz, J.: Centralbl. f. inn. Med., 1902, xxiii, 1161.

TABLE 4.—INCOAGULABLE NITROGEN FROM SCHULZ AND MÜLLER*

1.	Portal thrombosis, ascites	0.0306
	Same case	0.0371
	Same case	0.0252
	Same case	0.0322
	Same case	0.0273
	Same case	0.0217
	Same case	0.0280
	Same case	0.0217

*Schulz, O., and Müller, L. R.: Deutsch. Arch. f. klin. Med., 1903, lxxvi, 544.

TABLE 5.—INCOAGULABLE NITROGEN FROM EPPINGER'S TABLE*

No.	Diagnosis	Incoagulable Nitrogen in gm. per cent.
1.	Pleurisy, tuberculous	0.0630
2.	Pleurisy, tuberculous	0.03460
3.	Peritonitis, tuberculous	0.03587
4.	Pyopneumothorax	0.0406
5.	Pyopneumothorax	0.03640
6.	Carcinomatous pleuritis	0.07000
7.	Carcinomatous peritonitis	0.14000
8.	Ascites, cardiac	0.02700
9.	Ascites, cirrhosis of liver	0.0348

*Eppinger, H.: Ztschr. f. Heilk., 1904, xxv (Abt. f. Med.), 378.

TABLE 6.—INCOAGULABLE NITROGEN FROM GALDI'S TABLE*

No.	Diagnosis	Incoagulable Nitrogen in gm. per cent.
...	.....	
...	.....	
...	.....	
1.	Pleurisy, tuberculous	0.0563
2.	Peritonitis, tuberculous	0.0435
3.	Pleurisy, tuberculous	0.0300
4.	Chylous ascites, cancer of pancreas and liver	0.0896
5.	Ascites, cholelithiasis	0.0369
6.	Pleurisy, tuberculous	0.0208
7.	Cancer of peritoneum	0.0532
8.	Banti's disease with cirrhosis and ascites	0.0359
9.	Case 8, some weeks later (peritonitis?)	0.0406
10.	Polyserositis (peritoneal)	0.1064
11.	Cirrhosis of liver	0.0616
12.	Cancer of stomach and peritoneum	0.0448
13.	Case 12, five weeks later	0.0584
14.	Cancer of pleura	0.0602
15.	Cirrhosis of liver	0.07

*Galdi, F.: Clin. med. ital., Milano, 1905, xliv, 65.

TABLE 7.—INCOAGULABLE NITROGEN FROM ZAK'S TABLE*

No.	Diagnosis	Incoagulable Nitrogen in gm. per cent.
...	.....	
...	.....	
...	.....	
1.	Hydrothorax	0.04306
2.	Pleuritis	0.02792
3.	Pleuritis	0.01479
4.	Ascites, nephritic	0.04139
5.	Hydrothorax	0.01391
6.	Ascites, chronic peritonitis, cirrhosis	0.04515
7.	Ascites, cardiac	0.04113
8.	Pleuritis	0.02436
9.	Pleuritis	0.02368
10.	Ascites, ovarian cysts (?)	0.0266
11.	Ascites, tuberculous	0.03243
12.	Pleuritis	0.03133

*Zak, E.: Ueber Autolyse in Punktionsflüssigkeiten, Wien. klin. Wchnschr., 1905, xviii, 376.

TABLE 8.—GROUP I. INCOAGULABLE NITROGEN LESS THAN 0.0699 GM. PER CENT.*

From Table 1	21 observations on	20 fluids
From Table 2	2 observations on	2 fluids
From Table 3	6 observations on	6 fluids
From Table 4	8 observations on	1 fluid
From Table 5	7 observations on	7 fluids
From Table 6	12 observations on	11 fluids
From Table 7	12 observations on	12 fluids
Totals	68 observations on	59 fluids
Cancers—Group I	5 observations on	4 fluids

TABLE 9.—GROUP II. INCOAGULABLE NITROGEN 0.07 TO 0.0899 GM. PER CENT.*

From Table 1	1 observation on	1 fluid
From Table 3	1 observation on	1 fluid
From Table 5	1 observation on	1 fluid
From Table 6	2 observations on	2 fluids
Totals	5 observations on	5 fluids
Cancers—Group II	2 observations on	2 fluids

TABLE 10.—GROUP III. INCOAGULABLE NITROGEN 0.09 TO 0.1+

From Table 1	3 observations on 2 fluids
From Table 5	1 observation on 1 fluid
From Table 6	1 observation on 1 fluid
Totals	5 observations on 4 fluids
Cancers—Group III	4 observations on 3 fluids

0.07 to 0.0899 gm. per cent., and Group III 0.09 to 0.1 gm. or more. Using this classification, the majority of fluids fall in Group I, i. e., sixty-eight observations in fifty-nine fluids. Group II contains only five fluids, while in Group III there are five observations on four cases (see Tables 8, 9 and 10). In analyzing the three groups with reference to cancer, one finds that Group I includes four of cancer out of a total of fifty-nine fluids, Group II, two cases out of five, and Group III, three out of four. It would thus appear — though I realize that the statistics are too small to permit of generalizations — that a puncture fluid with incoagulable nitrogen below 0.07 gm. per cent. is *probably* not of malignant origin. In Group II, one's suspicions of malignant disease would be strongly aroused, while in Group III the probability of carcinoma would seem to be great. The single non-carcinomatous case included in Group III is one of "polyserositis" (No. 10, Table 6). In explanation of this finding, there appear to be at least two possibilities, either that a non-carcinomatous fluid occasionally shows a very large amount of incoagulable nitrogen, or that the case was in reality one of malignant disease.

No explanation of the high incoagulable nitrogen in certain carcinomatous fluids can be given at the present time. It is highly probable, however, that it is the result of the action of a proteolytic enzyme. (The fluids have been tested for the presence of preformed tryptophan with negative result.) It is possible, too, that an anti-enzyme may account for the low values met with in some of the cancerous fluids. Both of these points are under investigation. An attempt is also being made to determine whether the application of this method to the blood may be of service in the recognition of malignancy.

1806 Locust Street.

THE INFLUENCE OF TEMPERATURE ON THE OUTPUT OF THE HEART*

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While investigating the influence of the viscosity of the blood on the output of the heart, I observed that the cardiac discharge depends in a large measure on the temperature of the fluid used to vary the viscosity. This observation prompted me to disregard secondary effects for the present and to determine, first of all, the relationship between the temperature of the blood and the cardiac output.

The output of the heart was ascertained in accordance with the method of Rothberger.[1] The heart was placed in an oncometer of glass, the changes in the volume of the heart being recorded by air transmission. Rothberger confined his measurements to the changes in the ventricles, the volumetric variations of which were obtained by covering the large orifice of the oncometer with a rubber membrane and by inserting the organ up to its auriculoventricular junction through a central opening in the membrane. Rothberger employed still another procedure. He placed the entire heart in the oncometer and fastened the pericardial membrane over the brim of the instrument. Although actual values for the output of the heart cannot be obtained in this manner, it is nevertheless readily possible to record any change in the filling of the entire organ. As I sought to determine solely those alterations in the output of the heart and in the pulse-rate which are induced by varying the temperature of the blood, it was not my object to obtain precise quantitative data regarding the amount of the blood discharged by this organ. After all, the cardiac output is very much influenced by outside factors, for example, by the size of the animal, and the general condition of the heart and vascular system.

The experiments were carried out on cats in ether narcosis. The cavity of the chest having been opened, the pericardial sac was reflected and the heart placed in the oncometer. I made use of an ordinary Marey tambour instead of a piston recorder. The carotid artery was then connected with a mercury-manometer. Cannulas were inserted in the femoral artery and accompanying vein. A short time before the beginning of the experiment, a certain quantity of blood was withdrawn from a second

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1. Rothberger: Arch. f. d. ges. Physiol., 1907, cxviii, 358. A similar method was devised by Henderson: Am. Jour. Physiol., 1906, xvi, 325.

cat and its coagulation prevented by means of hirudin. Immediately before each experiment, the blood of the first animal was also rendered non-coagulable by injecting a sufficient amount of the same substance intravenously. A coil condenser was then filled with the blood obtained from the second animal. The ends of this coil were subsequently connected with the cannulas in the femoral blood-vessels, in such a way that the arterial blood traversed first of all the coil, before it again entered the circulatory system. A thermometer was placed in the venous end of the coil, for the purpose of determining the temperature of the blood as it entered the circulatory system. The temperature of the blood as a whole could readily be altered by passing water of different temperature through the jacket of the coil.

Naturally the temperature of the blood recorded at the femoral vein differs somewhat from that at the sinus of the heart, because as the blood in the coil soon meets the blood of the general circuit, the temperature must be higher at the latter point of the vascular system, and again, if the blood has been cooled, we would expect the temperature near the heart to be higher than that at the condensor. The changes in temperature occur gradually, but a certain variation cannot be avoided, because the velocity of the flow through the condensor also differs. The total amount of blood present in the animal always remains the same, because the quantity escaping from the femoral artery is again diverted into the vein.

The experiments have proved conclusively that the lowering of the temperature materially lessens the output of the heart. This effect is clearly shown in Figure 1. The upper record represents the volume of the heart as written by the cardiometer, and the lower record the carotid blood-pressure. The time is given in seconds. This line serves as the abscissa for the blood-pressure.

Although a diminution in the pulse-rate appeared as a rule in consequence of the decrease in the temperature, the difference was not always striking. In some of the tests a change in the systemic blood-pressure also resulted, but the change did not conform strictly to the temperature. While a lowering of the temperature usually led to a slight increase in the blood-pressure, it also happened that this procedure induced a moderate decrease. It was also evident that very slight differences in the temperature suffice to produce very pronounced alterations in the output of the heart. Even changes in the temperature of the blood which remained within physiological limits were sufficient to influence greatly the work of the heart. Herein lies the significance of this observation.

While employing the method described by Lohman,[2] Rothman[3] came to the conclusion that increases in temperature produce a similar change

2. Lohman: Arch. f. d. ges. Physiol., 1907, cxviii, 260.
3. Rothman: Arch. f. d. ges. Physiol., 1907, cxx, 400.

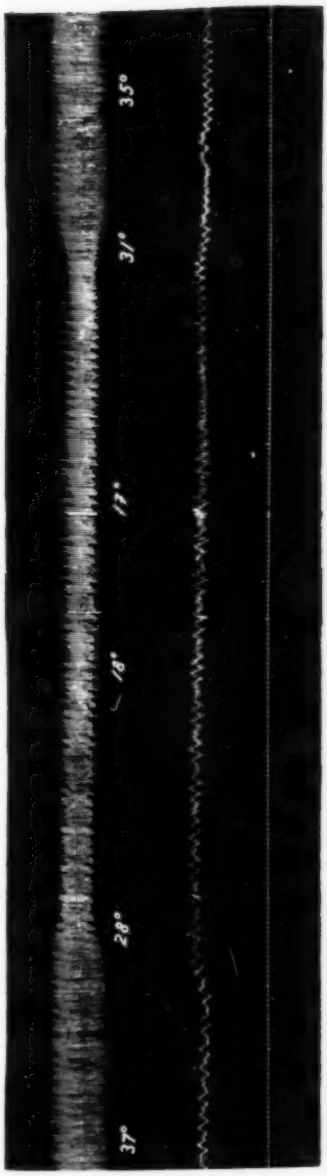

Fig. 1.—Infusion of cold blood. Pulse-rate 200 at 37 C. and 136 at 17 C. and again 164 at 35 C. The output decreases as the temperature is lowered and again increases. The blood-pressure is slightly increased.

in the pulse-rate and in the work of the heart, hence these factors bear a direct relationship to one another. Heglin[4] and also Winkler[5] obtained similar results by estimating the work of the heart in terms of intra-auricular blood-pressure. In accordance with Heglin, the efficiency of the heart is increased by cold and decreased by hot douches. Although confirmed by Winkler, this observation is not seconded by Strassburger. I mention these experiments, but realize that they have no direct bearing

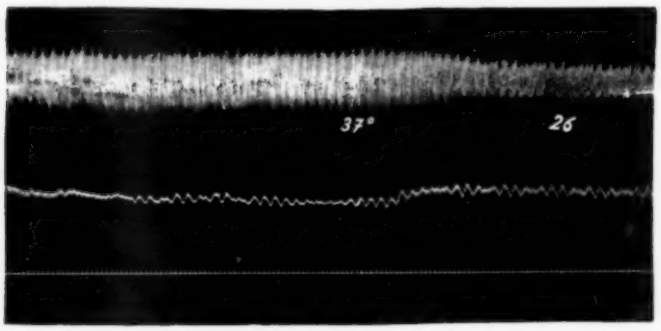

Fig. 2.—Both vagi were cut. Output decreased on cooling. Pulse-rate decreased from 220 to 160. Blood-pressure showed a slight rise.

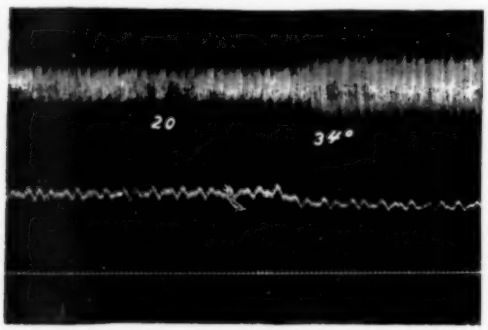

Fig. 3.—Both vagi were cut. Output increased on warming the blood. Pulse-rate increased from 160 to 184. Blood-pressure showed a slight fall.

on the question at issue here. In the first place, it is not proved that an actual change in the temperature of the blood results under the experimental conditions described in these papers and, secondly, numerous tests with isolated hearts have shown that the frequency of the beat varies with the temperature.

4. Heglin: Ztschr. f. klin. Med., 1894, xxvi, 15.
5. Winkler: Ztschr. f. klin. Med., 1904, liv, 92.

In endeavoring to find the cause of the variations in the cardiac discharge, I excluded, first of all, the influence of the nervous centers by severing both vagi. A comparison of the records taken before and after double vagotomy showed conclusively that this procedure has no influence on the cardiac output. A decided decrease was again obtained by cooling the blood, and an equally conspicuous increase by warming the blood. The changes here alluded to are clearly portrayed in Figures 2 and 3.

I also tested the effect of atropin in doses of $^1/_{100}$ to $^1/_{60}$ gr. The stimulation of the vagus nerve having become ineffective, the influence of changing the temperature of the blood was again determined as before. Results identical with those described previously were obtained.

The variations in the cardiac discharge and in the pulse-rate must, therefore, be dependent on a direct effect on the heart-muscle. The blood-pressure is not always affected in a manner corresponding to the temperature of the blood. When the temperature was lessened, the blood-pressure increased as a rule, while the warming of the blood was usually followed by a decrease. Evidently we are dealing in this case with a peripheral reaction, in that the cooling of the blood caused a constriction of the distal vascular channels and therefore also a rise in the general blood-pressure.

This fact is of importance in the treatment of infectious diseases, inasmuch as the work of the heart is a product of the output of the heart in a unit of time, in conjunction with the blood-pressure. The work of the heart increases, therefore, with the pulse-rate, the cardiac discharge and the blood-pressure. The results of these experiments permit the assumption that the work of the heart becomes greater during fevers, provided the blood-pressure remains constant. As fevers affect not only the peripheral blood-vessels but also those of the heart, the resulting impairment of the nutrition of this organ must become the more severe, the greater the increase in the work of the heart.

Mention must be made at this time of the investigation of Yoshimura,[6] who has proved by thermo-electrical methods that the ventilation of the lung has a cooling effect on the heart. The blood leaving the pulmonary veins possesses a lower temperature than the cardiac substance and exerts, therefore, a cooling influence on this organ. If the escape of heat from the cardiac surface is prevented by enclosing the organ in cotton, the temperature of the cardiac muscle rises several degrees and the pulse-rate increases considerably. When infectious diseases, and especially pneumonia, are treated in the open, the cool air entering the lungs lowers the temperature of the heart and lessens, therefore, the work of this organ by decreasing the cardiac output and the pulse-rate.

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6. Yoshimura: Arch. f. d. ges. Physiol., 1909, cxxvi, 239.

EXPERIMENTAL CARDIORENAL DISEASE*

HENRY A. CHRISTIAN, M.D., R. M. SMITH, M.D., AND
I. CHANDLER WALKER, M.D.
BOSTON

INTRODUCTION

HENRY A. CHRISTIAN, M.D.

During a period of about two years in the Laboratory of the Department of the Theory and Practice of Physic at Harvard we have been studying the lesions produced by certain chemicals known to have a particular action on the heart and kidneys. Different phases of this study have been undertaken by Dr. Smith, Dr. Walker and myself. In each case the topic has been studied by those whose names appear with the title and each study has been an independent one. However, as the topics are closely related and all form a part of a general investigation of cardiorenal disease, they are published together under the general title of Experimental Cardiorenal Disease as part of a series of studies of which three[1] have been published previously. It is hoped that by such a combined method of study—in the beginning, of experimental lesions, later, of the natural disease in man—some further light eventually may be thrown on that tangled complex which we frequently speak of clinically as cardiorenal disease. It will be evident to the reader of these papers that such a goal is far from attained, but some slight advance may be claimed from these experimental studies.

The general method followed in the present study has been to inject animals, chiefly rabbits, with varying doses of the drugs used, to follow the course of the disease so produced, and finally to autopsy the animals, preserving all of the tissues for histological study just as is done with human autopsy material in a well organized pathological laboratory. Particular attention has been paid to the heart, the kidney and the liver, though other tissues have been examined.

It has been quite evident to us that the substances used in this study, all of which have been employed by other investigators, have a remarkably

*From the Laboratory of the Department of the Theory and Practice of Physic, Medical School, Harvard University.

1. Study I.—Smith, R. M.: The Origin of Urinary Casts; An Experimental Study, Boston Med. and Surg. Jour., 1908, clviii, 696. Study II. Christian, Henry A.: A Glomerular Lesion of Experimental Nephritis; Boston Med. and Surg. Jour., 1908, clxix, 8. Study III. Christian, Henry A.: Clinical Value of Recent Studies in Experimental Nephritis; Jour. Am. Med. Assn., 1909, liii, 1792.

localized effect in that the marked action is on one organ with but slight action on other organs. Uranium nitrate, etc., have but little demonstrable action in producing lesions elsewhere than in the kidney, and so for spartein and adrenalin in relation to the heart. This makes it possible to control quite satisfactorily the experimental lesion. At the same time individual susceptibility in animals varies and other imperfectly understood factors enter to render difficult the regular production of chronic lesions, which in the main are what we must produce before animal experimentation will greatly aid us in obtaining knowledge of chronic cardiac and renal disease in man.

252 Marlborough Street.

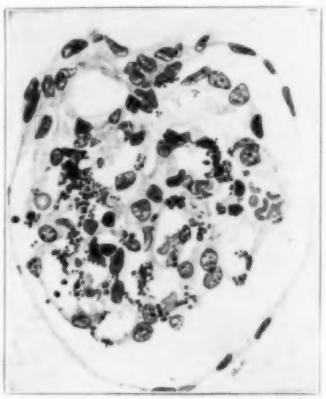

Fig. I.—Camera lucida drawing of a glomerulus showing the type of degenerative lesion commonly found in acute uranium nitrate nephritis in the rabbit.

STUDY IV. VASCULAR LESIONS OF ACUTE EXPERIMENTAL (URANIUM NITRATE) NEPHRITIS *

HENRY A. CHRISTIAN, M.D., BOSTON

In 1908, under the title "A Glomerular Lesion of Experimental Nephritis"† I described certain changes found in the glomeruli of the kidney in rabbits which had received subcutaneous injections of uranium nitrate. These changes were found in eleven of a series of thirteen rabbits treated in this way.

The lesion described at that time is essentially a vascular lesion affecting the capillaries of the glomerular tuft and consists of a type of hyaline

*From the Laboratory of the Department of the Theory and Practice of Physic, Medical School, Harvard University.

*Reported at the Annual Meeting of the Association of American Physicians, May 9-10, 1911, Atlantic City.

†Christian, Henry A.: Boston Med. and Surg. Jour., 1908, clix, 8.

degeneration of the wall of the capillary, as shown in Figure I.* The lesion was described as follows:

> The lesion consists of the appearance in the glomerular tuft of small, round or oval, rarely irregular, homogeneous droplets, varying from a half to four microns in diameter. These droplets appear in the wall of the capillaries making up the glomerular tuft, and do not occur either in the lumen of the capillaries or in the space between the glomerular tuft and the capsule of the glomerulus except in rare instances, when their position might be explained as an artifact in preparation. They were not found in the epithelium lining Bowman's capsule. In some glomeruli, only a few scattered droplets occur, while in others they are very numerous. Very often in a glomerulus they tend to occur in groups of three to six or eight, and where the larger groups are found, almost always some of the droplets are considerably coarser than others of the same group. In some rabbits almost every glomerulus contains many droplets of fairly large size; in others the droplets are uniformly smaller. In some rabbits, some glomeruli contain numerous droplets while adjacent glomeruli are free from them. This focal distribution seemed to have no relation to the other lesions of the kidney,

Fig. II.—Camera lucida drawing of a glomerulus from Rabbit 106 (acute uranium nitrate nephritis) showing fibrin thrombi in the capillaries of the glomerular loops.

> and no cause for it was to be made out. In kidneys showing slight degrees of the lesion, only here and there a glomerulus showed a few fine droplets . . . The droplets which are here described stain intensely blue black with Mallory's phosphotungstic acid hematoxylin (hematein) stain, and resist decolorization with ferric chlorid for a long time. With eosin and methylene-blue they stain pale red. The exact nature of the droplets is not known. Usually they can be distinguished quite easily from the somewhat more irregular granules associated with fibrin threads in the glomeruli.

As this degenerative lesion of the glomerular tuft is essentially a vascular lesion, and inasmuch as the recent studies of nephritis have tended to show that the edema of the disease is dependent on some vascular

*I am indebted to Miss Piotti for these drawings.

injury, and since the substance, uranium nitrate, which produces the above described glomerular lesion is the one which experimentally most frequently leads to the accumulation of fluid in the body cavities and subcutaneous tissues in association with renal lesions, it seemed desirable by a series of experiments to determine whether or not other demonstrable vascular lesions resulted from the use of uranium nitrate in rabbits. Consequently the following series of medium-sized rabbits were injected subcutaneously with 5 mg. of uranium nitrate at periods of twenty-four hours, as shown in the following protocols:

Rabbits 100 and 101 were injected subcutaneously March 27 with 5 mg. of uranium nitrate, and were killed twenty-four hours later.

Rabbits 102 and 103 were similarly injected on March 27 and 28, and were killed forty-eight hours after the first injection.

Fig. 1.—Rabbit 225; kidney shows slight irregularity of surface.

Rabbits 104 and 105 were similarly injected on March 27, 28 and 29, and were killed seventy-two hours after the first injection.

Rabbits 106 and 107 were similarly injected on March 27, 28, 29 and 30; Rabbit 106 was found dead ninety-six hours after the first injection, and Rabbit 107 was killed ninety-six hours after the first injection.

Rabbits 108 and 109 were similarly injected on March 27, 28, 29 and 30, and were killed 120 hours after the first injection.

Macroscopic Changes.—Of these rabbits, 100 and 101 showed at autopsy no departure from the normal. Rabbit 102 showed the usual amount of moisture in the body cavities, and scattered over the posterior portion of the peritoneal cavity numerous small subcutaneous hemorrhages of about pin-head size. Rabbit 103 showed a distinctly increased amount of moisture in the body cavities, and a small amount of free fluid

in the dependent portions of the peritoneal cavity. Rabbits 104 and 105 showed the same condition with respect to fluid, and in addition small hemorrhagic areas scattered in the peritoneal tissues. Rabbit 106 showed a moderate amount of free fluid in the peritoneal cavity. Rabbit 107 showed a very small amount of free fluid in the peritoneal cavity, and numerous small hemorrhagic points scattered over the surface of the kidney. Rabbits 108 and 109 showed a moderately increased amount of fluid in the body cavities.

Microscopic Changes.—The following microscopic changes were noted in the kidneys of these rabbits:

In Rabbit 100 very slight degenerative changes in the tubular epithelium were made out but no lesions in the glomeruli.

Fig. 2.—Rabbit 257, kidney; gross specimen shows marked granularity and irregularity of surface of kidney.

In Rabbit 101 there was a more marked degree of degeneration of the tubular epithelium amounting to necrosis of the epithelial cells lining scattered tubules, and the presence in the lumina of the tubules of casts composed of desquamated, degenerated epithelial cells and granular material. No glomerular lesions could be made out.

In Rabbit 102 degenerative changes such as those described in Rabbit 101 occurred, but in very much more marked degree. In the glomeruli there was quite frequently present a small amount of granular material in the capsular space. The walls of the capillaries of the

glomerular tuft appeared to be distinctly swollen. The lumina of the capillaries were usually less evident than in the preceding rabbits. The glomerular tuft gave the impression of an increased cellularity. However, no actual evidence of cell proliferation was found in the glomeruli, though in the tubules occasional mitoses were seen, indicating that reparative changes were in process in the epithelial cells of the tubules.

Rabbit 103 showed the same lesions as those described in Rabbit 102, but distinctly less marked in degree than in Rabbit 102, though slightly more extensive than those described in Rabbit 101.

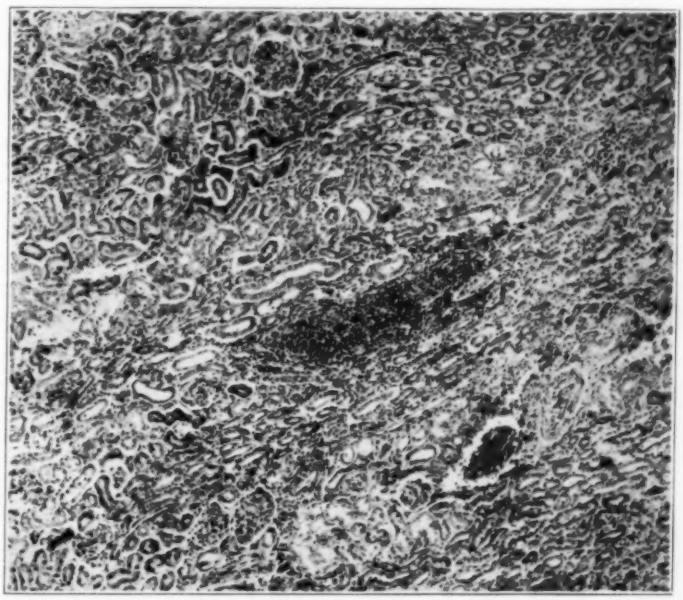

Fig. 3.—Rabbit 128. Kidney shows focus of marked cellularity infiltrated with neighboring focus of moderate connective tissue increase. Magnification 125 diameters.

Rabbit 104 showed the same changes as described in the preceding rabbits, and in degree about equal to that found in Rabbit 102. In addition, the glomeruli in Rabbit 104 showed scattered in the walls of the capillaries of the glomerular tuft hyaline droplets as described in my earlier report (see Fig. 1). These droplets were present in the majority of the glomeruli, and most of them were relatively coarse. In addition to these hyaline droplets staining darkly with the phosphotungstic acid hematein stain, the cytoplasm of the cells of the glomerular tuft was distinctly more granular than in the preceding animals. These granules

were fine, irregular, and stained rather palely compared with the droplets. They resembled the general appearance of granules ordinarily found in the epithelium lining tubules of the kidney where there is only a moderate degree of degeneration present.

Rabbit 105 showed a very slight degree of tubular degeneration, not more than that shown in Rabbit 101, and no lesion was seen in the glomeruli.

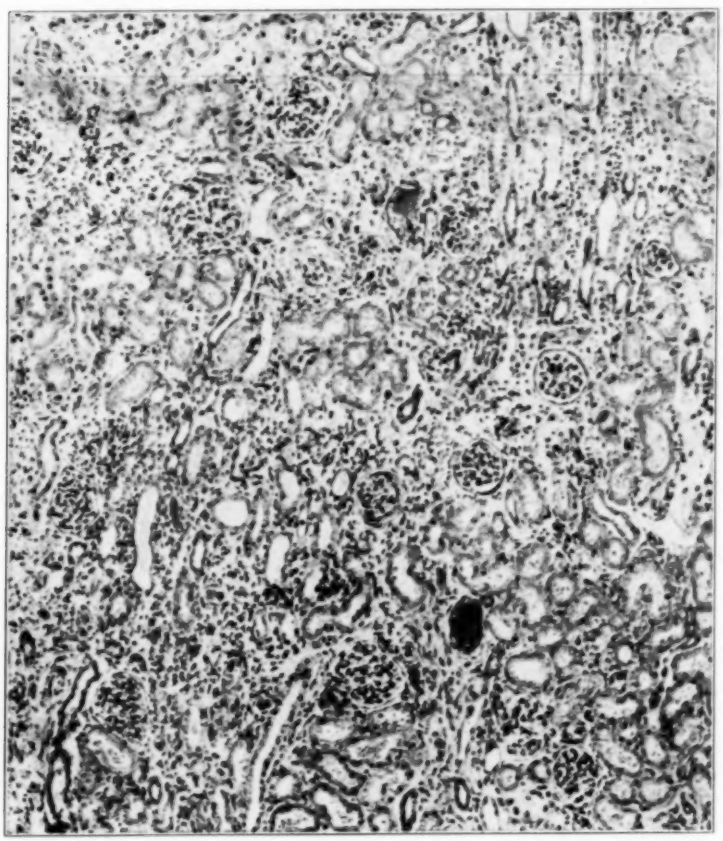

Fig. 4.—Rabbit 130. Kidney shows irregularly distributed areas of connective tissue increase in part fairly cellular. Magnification 146⅔ diameters.

In Rabbit 106 an extensive degree of degeneration and necrosis in the tubular epithelium were found. The glomeruli almost without exception showed the following lesion. The capillary loops nearly everywhere were filled with fibrin thrombi made up of rather coarse threads of fibrin which

very largely filled the lumen of the capillary as shown in Figure II. No hyaline droplets and no definite degenerative changes could be made out within the cells lining these capillaries. Except for the glomerular lesion, this kidney was similar to that from Rabbit 104. A lesion similar to this thrombosis of the capillary loops of the glomerulus was not found in any other of this series of rabbits, nor was it present in any of the other rabbits tabulated at the end of this paper. Up to the present time, no satisfactory explanation for this variation in lesion has been found, nor

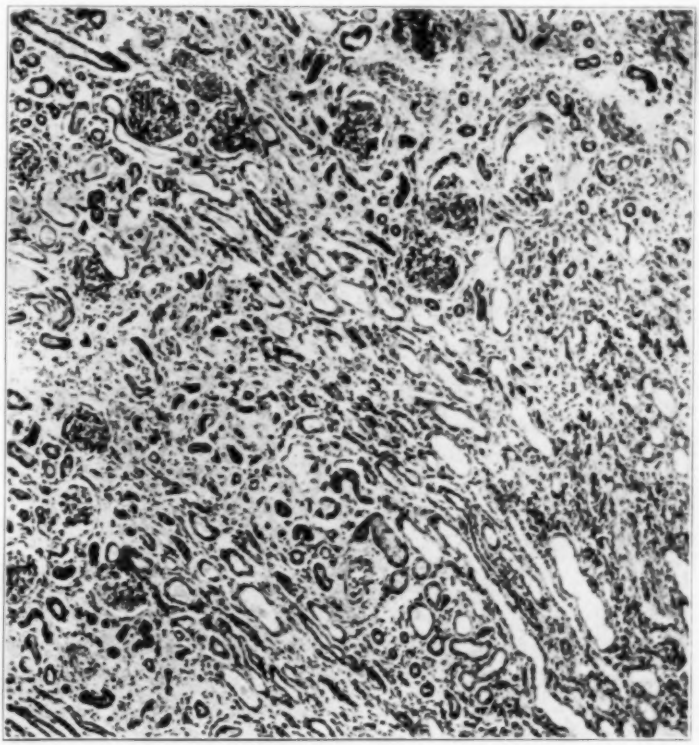

Fig. 5.—Rabbit 190. Kidney shows connective tissue increase with atrophy of tubules and sclerosis of glomeruli.

has it been possible to repeat this particular type of glomerular lesion by varying in several ways the conditions of the experiment.

In Rabbit 107 degenerative changes similar in nature to those described in Rabbit 104 were found. Hyaline droplets appeared in the glomerular tufts in the same way, but a rather larger percentage of glomeruli in Rabbit 107 failed to show the droplets than was the case in Rabbit 104.

Rabbit 108 showed extensive degenerative changes in the tubular epithelium, and the presence of many hyaline droplets in the walls of the glomerular tuft.

Rabbit 109 showed changes very similar to those described in Rabbit 108, including hyaline droplets in the walls of the glomerular tuft.

In this series of ten rabbits, definite vascular lesions occurred in the glomeruli of five animals. As a functional vascular injury has been assumed to be the cause of the edema of nephritis, it would seem probable that some demonstrable anatomical evidence of this lesion might be found by using the same technical method that demonstrates so well the above described glomerular lesion, a lesion hitherto overlooked. However, a

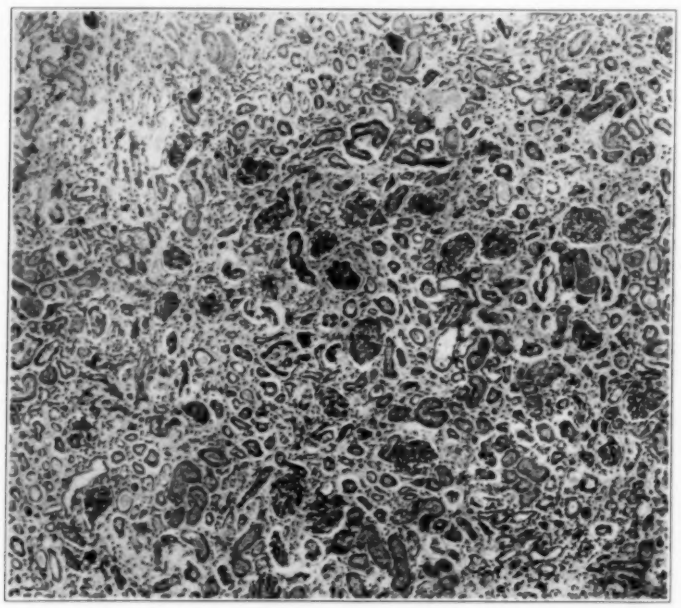

Fig. 6.—Rabbit 226. Kidney shows connective tissue increase.

very careful study of the small vessels of the kidney, other than those of the glomerular tuft, failed to show any demonstrable lesion, either with the phosphotungstic acid hematein stain, or with the eosin methylene-blue stain, or the elastic tissue stain of Verhoeff. In addition to the kidney, the heart, liver and the spleen were studied by these same methods, but no demonstrable lesion was found in the blood-vessels of any of these organs.

Small arteries and veins as well as capillaries in sections of tissues are not easy of examination, owing to their very thin walls which present

very little surface for study in any given section. In the capillary tuft of the glomerulus, the same conditions do not hold because there, with the convoluted course of the capillaries and the large number of loops aggregated together, a very considerable surface of capillary wall presents for examination. It seemed possible that this fact might be an explanation of finding anatomical lesions in the capillaries of the glomerulus and failing to find them in other vessels of relatively the same size.

In order to get small blood-vessels more suitable for microscopic examination, the mesentery was selected, inasmuch as here numerous small vessels run in an exceedingly thin tissue which, with proper precautions,

Fig. 7.—Rabbit 129. Kidney shows a focus of connective tissue increase with almost complete disappearance of the tubular structures and persistence in the glomeruli. Magnification 125 diameters.

can be prepared and stained without sectioning, so that a good view may be had of the small vessel in longitudinal optical section, thus revealing clearly all of the cells and tissue that go to make up the vessel-wall. Instead of cutting sections of this tissue, the mesentery was prepared by stretching it over the end of bottle tops and tying it in this position. The bottle top with the attached bit of mesentery was then fixed in Zenker's fluid and carried through the various staining procedures. Stretched over

the bottle top the mesentery was prevented from shrinking and remained flat and smooth. After the staining was completed and the mesentery dehydrated in alcohol, with fine scissors rectangular bits of the mesentery were cut away, cleared in xylol, and mounted in balsam, just as would be done with a celloidin section.

By selecting thin bits of the mesentery containing small blood-vessels, it was found possible to study very thoroughly the walls of such vessels. In them, however, no lesions in any way analogous to those found in the capillary tuft of the glomeruli could be made out. Since in these rabbits not infrequently there is a considerable amount of free peritoneal fluid,

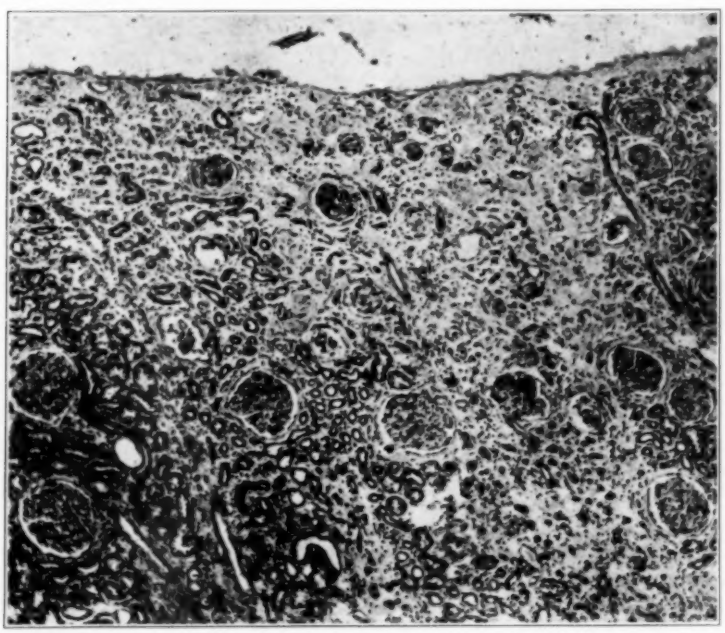

Fig. 8.—Rabbit 245. Kidney shows an area of quite dense connective tissue extending in from the surface of the kidney as a scar. This connective tissue very largely replaces renal elements. The glomeruli are more resistant than the tubules. Magnification 125 diameters.

it might be supposed that these vessels contributed to the accumulation of fluid, and in them should be found an anatomical lesion corresponding to this assumed functional lesion. However, this was not the case, or in other words, the methods of fixation and staining utilized did not succeed in demonstrating any anatomical lesion of these blood-vessels.

Thinking it possible that some larger blood-vessels might show a lesion, in all of these rabbits the aorta and inferior vena cava were ligated

so as to be distended with blood, and were fixed in Zenker's fluid in this condition. Subsequently, cross-sections of these distended vessels were embedded and stained in the various ways described above. Histological study of these, however, failed to show any anatomical lesion.

As a result of these studies, it is seen that the only anatomical lesion of the blood-vessels found in association with the renal lesions produced

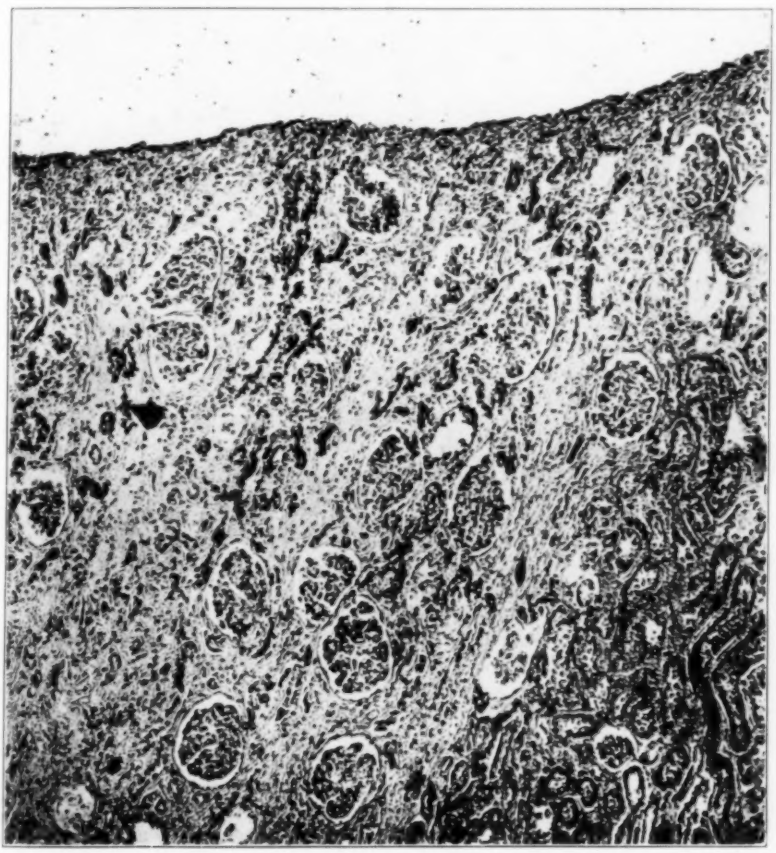

Fig. 9.—Rabbit 257. Kidney shows large area of connective tissue extending in from the surface as a scar. In this area the tubules have almost disappeared. The glomeruli are well preserved and situated close together as a result of the disappearance of the tubular structures. Magnification 146½ diameters.

by injections of uranium nitrate occurs in the glomerular tuft. The causal relation of this lesion to the uranium nitrate is shown in the following table, Table A, which gives the amount of uranium nitrate and the frequency of dose which produced this lesion in rabbits.

TABLE A.—RELATION BETWEEN LESIONS AND URANIUM NITRATE

No. of Rabbit	Weight of Rabbit gm.	No. of Doses of Uranium Nitrate	Total Amount of Uranium Nitrate gm.	No. of Days Between First Dose and Autopsy of Animal	No. of Days Between Last Dose and Autopsy of Animal	Lesion in the Glomerulus*
1	1350	3	.015	3	1	+
2	635	3	.012	3	1	+
3	825	3	.012	3	1	+
4	725	3	.012	3	1	+
5	1040	1	.005	1	1	0
6	730	2	.010	2	1	+
7	1020	1	.005	5	5	+
8	720	1	.004	4	4	+
9	930	2	.004	6	4	+
10	800	3	.003	17	21	0
11	985	1	.001	6	6	+
21	1950	1	.001	6	6	+
22	....	9	.013	110	15	0
71	2095	4	.0035	130	11	0
72	....	1	.001	6	6	0
73	....	1	.001	5	5	0
100	....	1	.005	1	1	0
101	....	1	.005	1	1	0
102	....	2	.010	2	1	0
103	....	2	.010	2	1	0
104	....	3	.015	3	1	+
105	....	3	.015	3	1	0
106	....	4	.020	4	1	+
107	....	4	.020	4	1	+
108	....	4	.020	5	2	+
109	....	4	.020	5	2	+
123	....	5	.021	6	1	+
198	1190	1	.005	5	5	0
199	1140	1	.005	5	5	0
200	1190	1	.005	5	5	+
221	1460	22	.044	90	21	0
226	1310	7	.014	33	2	0
240	2800	1	.005	6	6	+
249	1720	4	.020	60	3	0
251	1690	1	.005	7	7	+
259	1500	4	.008	18	7	0
190	1390	3	.015	44	11	0
128	....	2	.010	33	16	0

*The lesion here referred to is the occurrence of hyaline droplets in the wall of the capillary of the glomerulus as described above. The only exception to this is in Rabbit 106, where the lesion consists of the occurrence of fibrin thrombi in the capillaries of the glomerulus.

SUMMARY

In acute experimental nephritis produced by subcutaneous injections of uranium nitrate, there occurs in the glomerulus a degenerative condition consisting usually of the appearance of hyaline droplets of varying size in the wall of the capillary. In the other small vessels of the kidney and the small vessels of the heart, liver and spleen, and in the small vessels of the mesentery, no anatomically demonstrable lesion could be made out. The vascular lesion of this type of acute nephritis, as far as

could be demonstrated by the technical methods employed, is confined to a vascular structure of specialized function, a more highly differentiated structure than that of other small blood-vessels, namely, to the capillary loops of the glomerulus.

STUDY V. EXPERIMENTAL CHRONIC NEPHRITIS *

R. M. SMITH, M.D., BOSTON

The literature of experimental nephritis has been so recently and so fully discussed by Christian,[2] Pearce,[3] and others,[4] that I shall not enter into any consideration of it here; nor shall I discuss the problems arising in connection with the experimental work. In the course of the investigations cited in this paper many acute lesions were produced; animals died before chronic lesions were formed, or the acute lesion obscured the picture of a coincident chronic process. The study of these acute conditions has not shown anything new, and therefore their consideration is omitted. It has been possible, however, to produce certain chronic changes in the kidney, which I shall describe in some detail, together with an account of the methods employed in their formation.

The experiments were carried on in the laboratory of the Department of the Theory and Practice of Physic, under the direction of Dr. Henry A. Christian. The animals used were rabbits and guinea-pigs. The latter in my hands proved very unsatisfactory; the greater part of the work is therefore based on the lesions as seen in rabbits. Ninety-five animals were employed; eighteen were carried through a period of three weeks to three months, and fifty-six through a period of three months or over. The remainder died of acute lesions or of some intercurrent disease, usually pneumonia. Most of the animals were allowed to go a number of weeks without injection previous to killing to exclude any acute lesion.

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*From the Laboratory of the Department of the Theory and Practice of Physic, Medical School, Harvard University.

*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

2. Christian: Experimental Nephritis, Boston Med. and Surg. Jour., 1908, clviii, 416; Clinical Value of Recent Studies in Experimental Nephritis, Jour. Am. Med. Assn., 1909, liii, 1792.

3. Pearce: Problems of Experimental Nephritis, THE ARCHIVES INT. MED., 1910, v, 133.

4. Dickson: A Report on the Experimental Production of Chronic Nephritis in Animals by the Use of Uranium Nitrate, THE ARCHIVES INT. MED., 1909, iii, 375. Emerson: An Experimental and Critical Study of the Etiology of Chronic Nephritis, THE ARCHIVES INT. MED., 1908, i, 485. Lyon: Experimental Nephritis, Jour. Path. and Bacteriol., 1904, ix, 400. Ophüls: Some Interesting Points in Regard to Experimental Nephritis, Jour. Med. Research, 1908, xiii, 497. Ophüls: Chronic Experimental Nephritis, Jour. Am. Med. Assn., 1907, xviii, 483.

Three drugs were used: uranium nitrate, potassium bichromate and arsenic, in the form of Fowler's solution. No other drugs were tried because it was felt that it would be best to have a larger number of observations of lesions produced by a few drugs, from which more accurate conclusions might be drawn.

The question of dosage was a matter to which considerable attention was given and no little experimentation. It was found for a rabbit of average weight (1,500 to 2,000 gm.) 5 mg. of uranium nitrate was as much as it was safe to give, since larger doses killed the animals in many

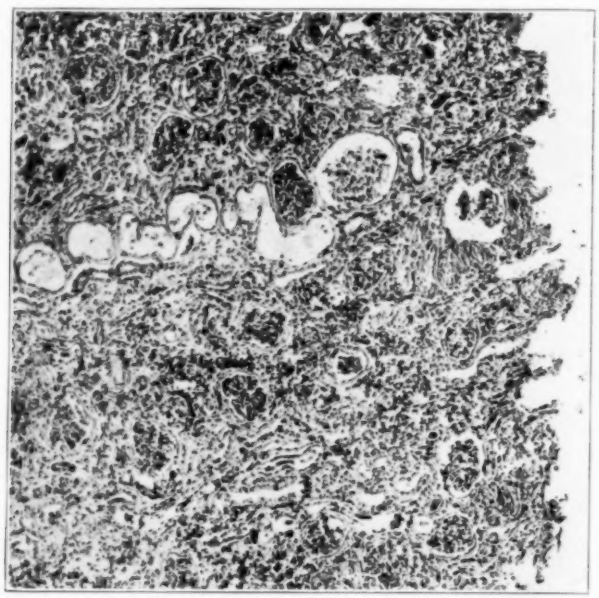

Fig. 10.—Rabbit 129. Kidney shows marked dilatation of one tubule, moderate dilatation of the glomerular space in one glomerulus, with surrounding connective tissue increase and atrophy of tubules.

instances. This dose gave a rather severe acute nephritis, but the great majority of the animals survived. By following the first-used animals very carefully it was found that in about three weeks the urine was nearly normal, i. e., the attack of acute nephritis was nearly over. This interval, three weeks, was taken, therefore, as the time at which the injections were to be repeated. Another method of employing this drug was to give very frequent small doses. For this purpose 2 mg. every three days were used. The comparative results of the two methods of injection will be discussed later. Potassium bichromate was used in a 1 per cent. solution. Here also the size and frequency of dosage was determined by experimentation.

and 0.0125 gm. of potassium bichromate every three weeks was decided on as the most satisfactory. Fowler's solution was given in from 8 to 10 minim doses, subcutaneously, and by stomach-tube, repeated every three weeks.

In guinea-pigs, for some reason or other, it was impossible to use the doses of uranium nitrate reported by others. More than 0.5 mg. for an average-sized guinea-pig was fatal in most cases. One-half milligram every three weeks was therefore used. Perhaps the smallness of the dose in some measure accounts for the unsatisfactory results. Bichromate of

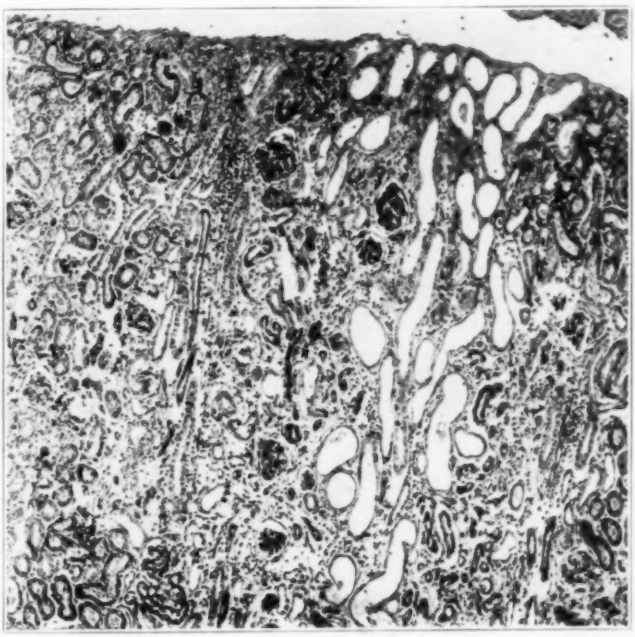

Fig. 11.—Rabbit 221. Kidney shows area of connective tissue increase with marked dilatation of a group of tubules. Magnification 125 diameters.

potassium was given, 0.005 gm. every three weeks. No guinea-pigs were tried on Fowler's solution.

Beside the animals used in these experiments, fifty rabbits were studied to exclude the possibility of the conditions described being due to spontaneous lesions. Some lesion was found in eleven of these fifty rabbits, or 20 per cent. The lesions when found consisted in almost every instance of a single area of round-cell infiltration, connective tissue increase or a small group of dilated tubules. Six of the sections showed such a slight variation from normal as to be practically negligible.

Another showed nothing but a connective tissue increase. Two showed moderate dilatation of tubules, but little else. The remaining two showed well-marked lesions—one of the animals had had intravenous injections of spartein sulphate and adrenalin (epinephrin) chlorid every day for two months. The experimental rabbits having uranium nitrate and potassium bichromate injections running over three months from the time of the first injection to the time of autopsy, thirty-nine in number, showed lesions of one form or another in thirty-six cases or 92.3 per cent. Seven guinea-pigs were similarly treated and four or 57.1 per cent. showed lesions. The percentage of experimental rabbits having lesions is so large,

Fig. 12.—Rabbit 268. Section shows myocardium with marked congestion of capillaries. Magnification 185 diameters.

the percentage of controls with lesions so small and the lesions so insignificant when present, that it makes it impossible to assume that the lesions in the experimental animals were other than the result of the injections given. The chronic lesions caused by uranium nitrate and potassium bichromate were the same, and will therefore be described together.

Three side-studies, so to speak, were made on this series of animals: (1) the weights of heart and kidneys in relation to the body-weight of the

animal and in relation to each other; (2) the effect of sodium chlorid and water in the production of edema; (3) a functional test in excreting phenolsulphonephthalein. These investigations are considered separately in other papers and are therefore only mentioned here.

The kidneys, macroscopically, were, in most cases, normal in appearance and in all the capsule stripped easily. On section the markings were distinct and the cortex not narrowed. In some the surface was covered with many irregular, smaller and larger depressions and on section bands of fibrous tissue could be seen running down into the substance of the organs. These macroscopic lesions occurred principally in the animals

Fig. 13.—Rabbit 266. Section shows a portion of myocardium with interstitial edema and moderate connective tissue increase. Magnification 185 diameters.

that had received potassium bichromate (Rabbit 225, Fig. 1, and Rabbit 257, Fig. 2).

Microscopically variations from the normal were seen in three main particulars. The most frequent abnormality was round-cell infiltration. This occurred in the animals which had received uranium and bichromate injections, but most consistently in those receiving the large doses of uranium. The areas of infiltration, though often very small, were frequently of considerable size. Their location was variable, but they were

most often found in the cortex and in the larger number of cases near the periphery (Rabbit 128, Fig. 3, also Rabbits 177, 189 and 195).

Beside this infiltration of round cells, in a certain number of animals there was formation of definite connective tissue. The connective tissue for the most part was fairly young (Rabbit 130, Fig. 4), but in some instances was old, having gone on to a fibrous tissue stage (Rabbit 190, Fig. 5, and Rabbit 226, Fig. 6). The distribution of the connective tissue was usually near the periphery of the organ. It often was so extensive as to replace entirely the tubular portion of the kidney over considerable areas, leaving a few tubules in the center as a small island (Rabbit 129,

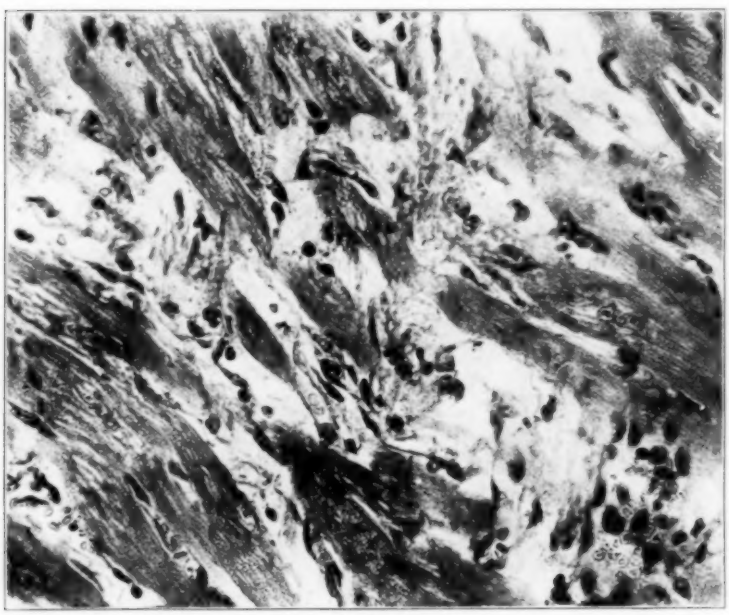

Fig. 14.—Rabbit 79. Section shows moderate connective tissue increase, edema, and moderate cellular infiltration of the myocardium. Magnification 185 diameters.

Fig. 7). Usually in sections showing an increase in connective tissue the connective tissue was seen as triangular foci running into the substance of the organ from the periphery with the apex inward. It was these fibrous bands which were found in connection with the macroscopic depressions on the surface of the kidney (Rabbit 245, Fig. 8, 257, Fig. 9; see also Rabbits 124, 207, 208 and 264).

The most distinctive lesion which was found, a lesion closely resembling that associated with chronic interstitial nephritis in man, was a

dilatation of the convoluted tubules and glomerular spaces. This occurred for the most part in sections which showed the other two conditions and most frequently in those animals which had had large doses of the drugs. The dilatation was patchy in distribution as were the areas of round-cell infiltration and was most often located in that portion of the cortex directly beneath the capsule. The glomerular spaces showed much less dilatation than the tubules (Rabbits 129, Fig. 10, and 221, Fig. 11; see also Rabbits 192, 193 and 196).

In the animals which had received arsenic, macroscopic examination of the kidneys showed nothing abnormal. Microscopically the kidney

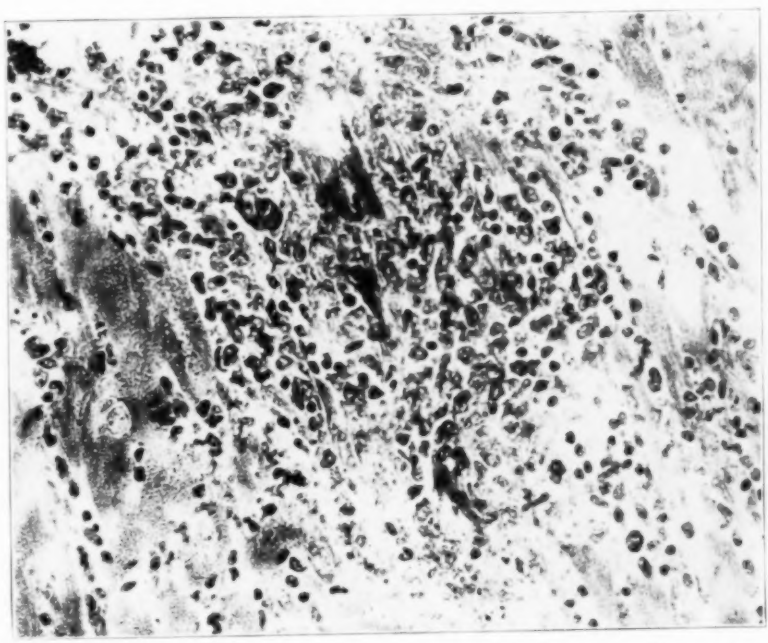

Fig. 15.—Rabbit 279. Section shows a very cellular focus of proliferation in the myocardium. Magnification 185 diameters.

sections from animals which had received the drug by mouth showed nothing, and in those given subcutaneous injections the only change seen was distinct congestion of the glomeruli without any apparent damage to the endothelium. In the cases where no injection had been given for a long time there was a little increase in the number of cells in the glomeruli. These findings are in accord with the reports of other investigators (Rabbits 233, 238, 243).

To reiterate in conclusion, to produce the more distinctive lesions of chronic interstitial nephritis experimentally the best results will be obtained by using as large doses of uranium nitrate and potassium bichromate as the animals will stand, repeated at three week intervals for three months or longer. Bichromate of potassium produces more fibrous tissue formation with macroscopic depressions on the surface of the kidney than uranium nitrate. Small frequent doses of uranium nitrate cause patchy round-cell infiltration throughout the cortex of the kidney and much increase in connective tissue. Arsenic produces no chronic macroscopic or microscopic lesion of the kidney, except congestion and slight increase of cells of the glomeruli.

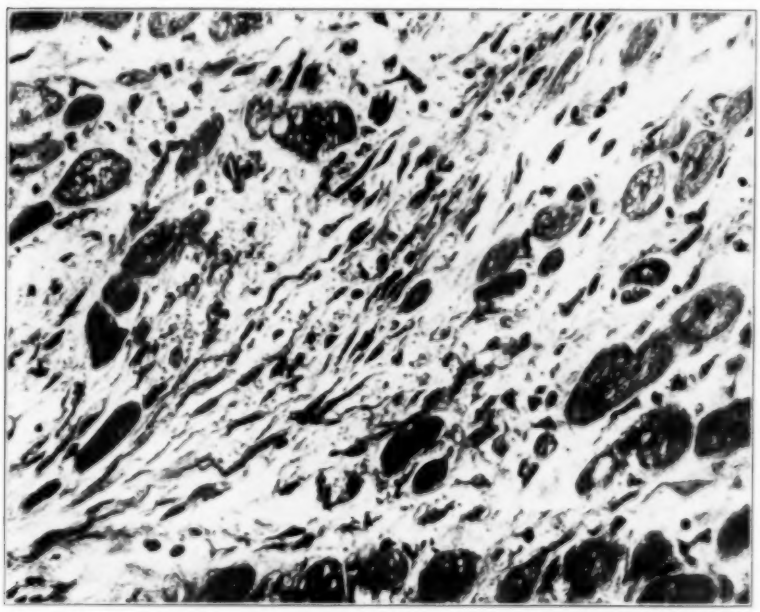

Fig. 16.—Rabbit 82. Section shows myocardium infiltrated with new connective tissue, fairly cellular, which separates muscle fibers. Magnification 185 diameters.

The protocols of the animals follow.

Protocol 124.—Rabbit. Weight 1870. Caged October 12. On 13th given 0.001 gm. uranium nitrate. Same on October 14, 15, 16, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29. On 30th 0.002 gm. of same. Same on November 1, 2, and every third day until February 10. Killed May 12.

Functional Test.—Twenty-five per cent. of phenolsulphonephthalein given, excreted in one hour.

Autopsy.—Excess of fluid in pericardial cavity, which was bulging. No edema elsewhere. Heart weight 5.75 gm. Kidneys, weight 11.55 gm., macro-

scopically normal. Microscopically scattered everywhere through the section and in many places surrounding a small collection of tubules, connective tissue is found in excess of normal and containing many lymphoid cells. In these areas of connective tissue there are a few dilated tubules and an occasional dilated glomerular space.

PROTOCOL 128.—Rabbit. Weight 1330. Caged November 16. On 17th given 0.005 gm. uranium nitrate. Repeated on December 8. Found dead December 20.

Autopsy.—No edema. Lungs show consolidation. Macroscopically other organs normal. Kidney microscopically shows areas of round cell infiltration with some increase in connective tissue; little dilatation of tubules and glomerular spaces.

PROTOCOL 129.—Rabbit. Weight 1520. Caged October 12. On 13th given 0.001 gm. uranium nitrate. Repeated October 14, 15, 16, 18, 19, 20, 21, 22, 23,

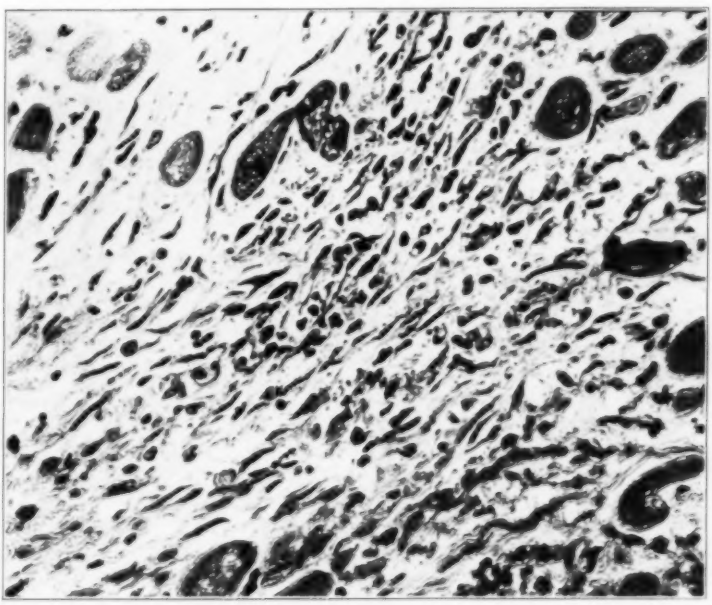

Fig. 17.—Rabbit 82. Section shows a fairly large, quite cellular area of connective tissue over the myocardium. Magnification 185 diameters.

25, 26, 27, 28, 29. On October 30 given 0.002 gm. same, repeated every third day until February 10. Died April 7.

Autopsy.—No edema. Heart weight 3.8 gm. Kidneys, weight 7.2 gm., macroscopically show no change. Microscopically there is an increase in connective tissue which entirely replaces the tubules in some places except for a few left in its midst. Some of this connective tissue is fairly cellular. In the areas of fibrous tissue there are some dilated tubules and occasional dilated glomerular spaces.

PROTOCOL 130.—Rabbit. Weight 2000. Caged October 12. On 13th given 0.001 gm. uranium nitrate. Repeated October 14, 15, 16, 18, 19, 20, 21, 22, 23, 25, 26, 27, 28, 29, and October 30 given 0.002 gm. of same and repeated every third day until February 10. Killed March 24.

Autopsy.—No edema. Heart weight 5 gm. Kidneys weight 10.2 gm., cortex pale; microscopically there is very slight recent destruction of the tubules; in many areas there is connective tissue increase with dilatation of tubules and some glomerular spaces.

PROTOCOL 177.—Rabbit. Weight 1250. Caged November 9. On 10th given 0.004 gm. uranium nitrate. Repeated December 2, 23, January 13, February 3, 24. Killed May 7.

Functional Test.—From 40 to 50 per cent. of phenolsulphonephthalein excreted in one hour.

Autopsy.—No edema. Heart weight 3.91 gm. Kidneys, weight 11.75 gm., macroscopically normal; microscopically marked patchy and diffuse round-cell infiltration, mostly in the cortex, but also in the medulla; many bands and patches of connective tissue often running in from the periphery and containing

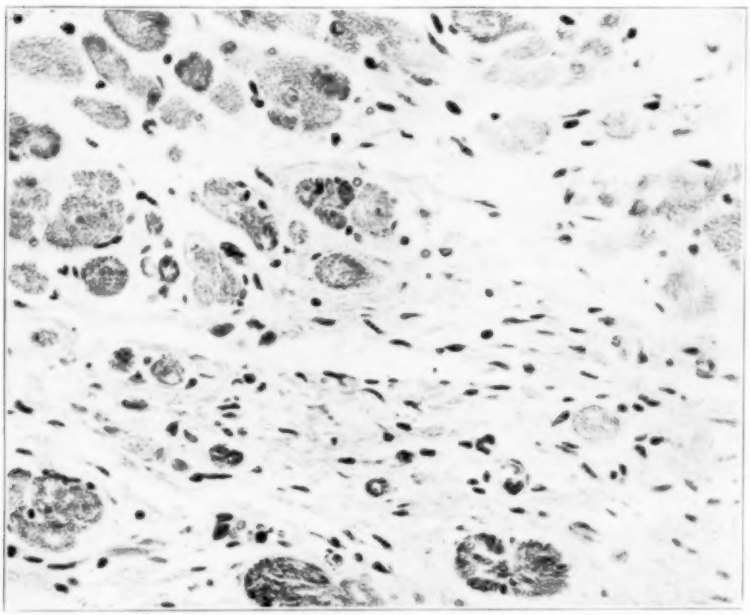

Fig. 18.—Rabbit 68. Section shows rather large focus of fairly dense connective tissue surrounding a small blood-vessel and infiltrating between adjoining muscle fibers. Magnification 185 diameters.

dilated tubules in considerable numbers; some of the glomerular spaces are also greatly dilated.

PROTOCOL 189.—Rabbit. Weight 1400. Caged November 16. On 17th given 0.005 gm. uranium nitrate. Repeated December 8, 31, January 20, February 14, March 11, 28. Killed April 27.

Functional Test.—Fifty per cent. of phenolsulphonephthalein excreted in one hour.

Autopsy.—No edema. Heart weight 5.5 gm. Kidneys, weight 12.9 gm., macroscopically many white specks on surface, microscopically marked increase in lymphoid cells scattered irregularly throughout the section and often very diffusely; some increase in connective tissue and a little dilatation of the tubules.

PROTOCOL 190.—Rabbit. Weight 1390. Caged November 16. On 17th given 0.005 gm. of uranium nitrate. Repeated on December 8 and 31. Died January 11.

Autopsy.—No edema. Heart weight 3.31 gm. Kidneys, weight 12.85 gm., macroscopically large and soft; microscopically show rather diffuse connective tissue increase replacing tubules in some places, especially marked at junction of cortex and medulla; very little dilatation of tubules.

PROTOCOL 192.—Rabbit. Weight 1470. Caged November 18. On 19th given 0.005 gm. uranium nitrate. Repeated December 11, January 3, 25, March 11, 28, and killed April 30.

Functional Test.—Slight delay in excretion of phenolsulphonephthalein.

Autopsy.—No edema. Heart weight 3.4 gm. Kidneys weight 8 gm. Macroscopically normal. Microscopically many small scattered patches of round-cell infiltration, many bands of connective tissue running from the periphery and

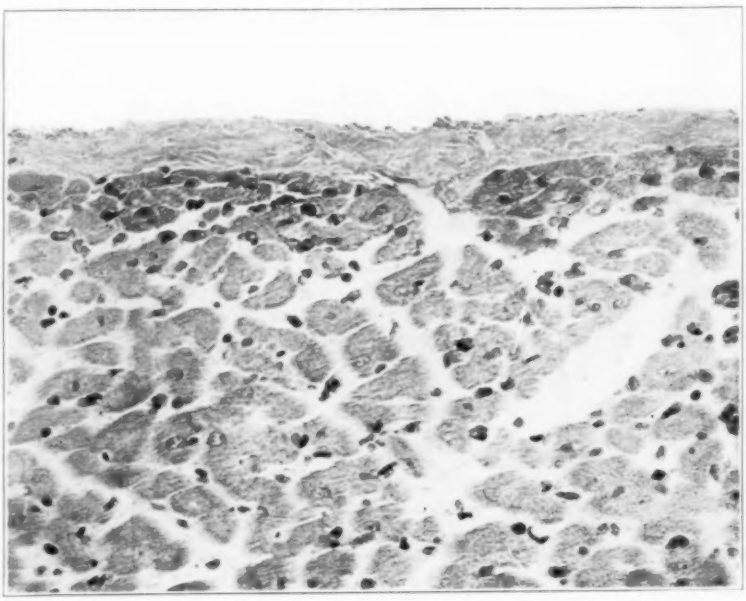

Fig. 19.—Rabbit 273. Section shows normal pericardium with slight hemorrhagic exudation and congestion of subpericardial myocardium. Magnification 185 diameters.

patches scattered elsewhere in cortex. In this there is also an infiltration of lymphoid cells and many dilated tubules.

PROTOCOL 193.—Rabbit. Weight 2500. Caged November 18. On 19th given 0.005 gm. uranium nitrate. Repeated December 11, January 1, 23, February 17, March 11, 28. Died April 29.

Autopsy.—No edema. Heart weight 8.4 gm. Kidneys weight 14.9 gm. Macroscopically normal. Microscopically, considerable round-cell infiltration, situated almost entirely in bands running in from the periphery. In these areas much increase of connective tissue and sometimes in the medulla. In the strips of connective tissue, often very extensive, there is marked dilatation of the tubules. Some dilatation of tubules and glomeruli elsewhere.

PROTOCOL 195.—Rabbit. Weight 1200. Caged November 18. On 19th given 0.005 gm. uranium nitrate. Repeated December 11, January 1, 23, February 14, March 11, killed on March 27.

Functional Test.—Fifty per cent. of phenolsulphonephthalein excreted in one hour.

Autopsy.—No edema. Heart weight 3.5 gm. Kidneys, weight 12.1 gm., capsule strips easily; microscopically very marked round-cell infiltration in long bands running from the cortex and in scattered patches; very little connective tissue increase or dilatation of the tubules or glomeruli.

PROTOCOL 196.—Rabbit. Weight 1200. Caged November 22. On 23d given 0.005 gm. uranium nitrate. Repeated December 16, January 6, 27, February 17, March 11, 28.

Functional Test.—Thirty per cent. of phenolsulphonephthalein excreted in one hour.

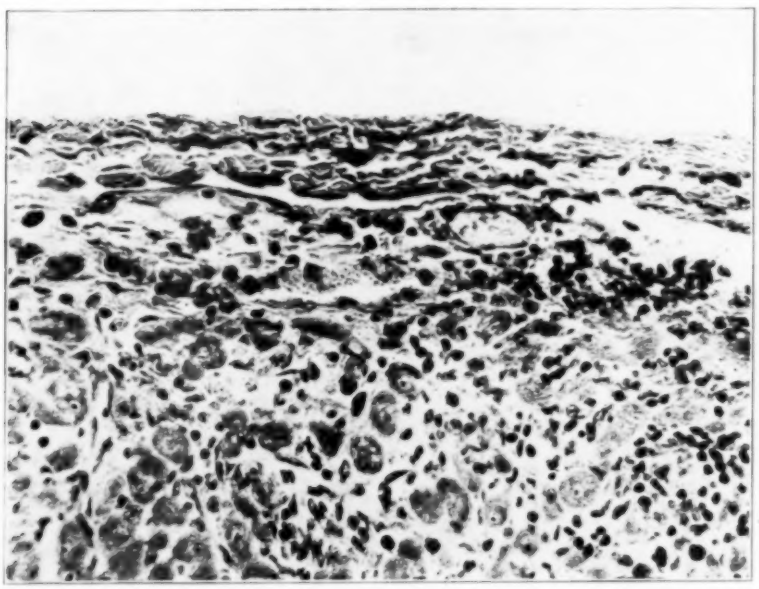

Fig. 20.—Rabbit 279. Section shows thickening of pericardium with increased cellularity of pericardium and myocardium. Magnification 185 diameters.

Autopsy.—No edema. Heart weight 4.5 gm. Kidneys, weight 13 gm. On section cortex very pale. Microscopically scattered throughout the section there are a few small patches of lymphoid cells. Great amount of connective tissue formation, entirely replacing the tubules in some portions of the cortex. In the connective tissue usually near the periphery, but also present in the deeper portions are many dilated glomerular spaces.

PROTOCOL 207.—Rabbit. Weight 1530. Caged December 2. On 3d given 0.005 gm. uranium nitrate. Repeated every third day until March 28. Killed April 28.

Functional Test.—Sixty per cent. of phenolsulphonephthalein excreted in one hour.

Autopsy.—No edema. Heart weight 4.2 gm. Kidneys, weight 9.6 gm., cortex strips easily, very pale on section, otherwise normal. Microscopically the capsule and cortex beneath is very irregular in outline with some connective tissue increase often running in from the depressions; some round-cell infiltration in the newly-formed connective tissue and in small patches elsewhere, some dilatation of the tubules and glomeruli, especially the latter.

PROTOCOL 208.—Rabbit. Weight 1740. Caged December 2. On 3d given 0.005 gm. uranium nitrate. Repeated every third day until March 28. Killed April 28.

Functional Test.—Very slight excretion of phenolsulphonephthalein in one hour, too small to estimate.

Autopsy.—Excess of fluid in all body cavities. Heart weight 6.42 gm. Kidneys, weight 11.95 gm., macroscopically normal, capsule strips easily. Micro-

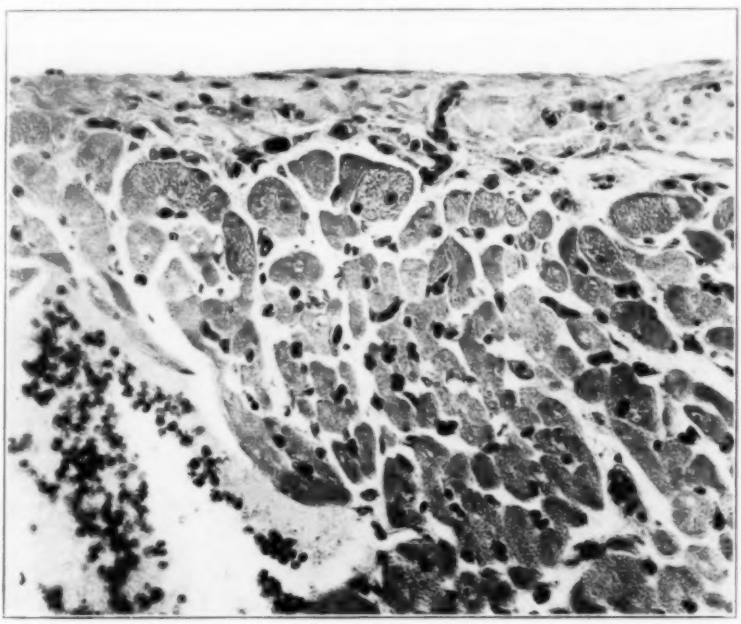

Fig. 21.—Rabbit 268. Section shows slight thickening of pericardium with slight edema and congestion of vessels of pericardium and myocardium. Magnification 185 diameters.

scopically very little round-cell infiltration, but marked increase of connective tissue. Some portions of the section show no tubules, the whole field being made up of connective tissue. Frequently small islands of tubules may be seen in the mass of surrounding tissue. Scattered diffusely through the organ are some slightly dilated tubules.

PROTOCOL 221.—Rabbit. Weight 1460. Caged December 2. On 3d given 0.005 gm. uranium nitrate. Repeated every third day until March 21. Killed March 24.

Autopsy.—No edema. Heart weight 4.4 gm. Kidneys, weight 11.6 gm., macroscopically appear normal; microscopically show patches of infiltration

with round cells and areas of increase in connective tissue. There is considerable dilatation of the tubules in groups or bands and some glomerular spaces are also much increased in size.

PROTOCOL 225.—Rabbit. Weight 1700. Caged December 6. On 7th given 21 minims 1 per cent. solution potassium bichromate. Repeated December 31, January 22, February 10, March 3. Killed March 24.

Autopsy.—Slight amount of straw-colored fluid in the abdominal cavity, none in thoracic cavity. Heart weight 5.7 gm. Kidneys, weight 12.5 gm., macroscopically normal, except for small depressions on the surface; microscopically there are small strips of connective tissue running in from the depressions on the surface, in which there is considerable round-cell infiltration. No dilatation of the tubules or glomeruli.

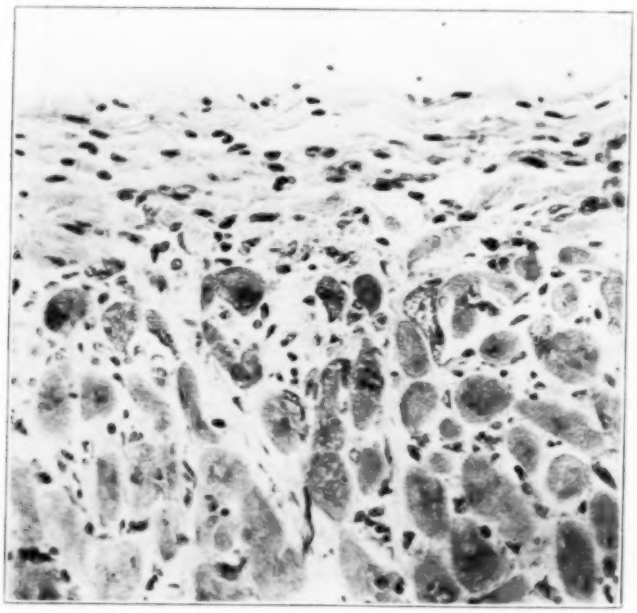

Fig. 22.—Rabbit 270. Section shows slight thickening of pericardium with increased cellularity of pericardium and myocardium. Magnification 185 diameters.

PROTOCOL 226.—Rabbit. Weight 1310. Caged December 6. On 7th given 0.002 gm. uranium nitrate. Repeated December 11, 23, 31, January 3, 6, 10. Found dead January 12.

Autopsy.—Kidneys microscopically, considerable increase in connective tissue with consequent disappearance of tubules. Some of the connective tissue is fairly cellular, other portions much less so. There are a few patches of dilated tubules.

PROTOCOL 233.—Rabbit. Weight 1600. Caged December 16. On 17th given 8 minims Fowler's solution subcutaneously. Repeated December 23, January 3, 10, 17, 25, February 3, 14, 24, March 12. Killed April 28.

Functional Test.—From 60 to 90 per cent. phenolsulphonephthalein excreted in one hour.

Autopsy.—No edema. Heart weight 5.3 gm. Kidneys, microscopically are normal, except for congestion of glomeruli and some increase in cellular elements.

PROTOCOL 238.—Rabbit. Weight 1730. Caged December 16. On 17th given 8 minims Fowler's solution by stomach tube. Repeated December 23, January 3, 10, 17, 25, February 3, 14, 24, March 12, killed May 12.

Functional Test.—Sixty per cent. phenolsulphonephthalein excreted in one hour.

Autopsy.—No edema. Heart weight 5.55 gm. Kidneys, weight 11.15 gm., macroscopically show a few pin-point hemorrhagic spots with slight depressions. Microscopically a few small patches of round-cell infiltration. Glomeruli very much congested with some increase in the cells.

PROTOCOL 243.—Rabbit. Weight 2280. Caged January 1. On 3d given 10 minims Fowler's solution subcutaneously. Repeated on 10th and 17th. Found dead on 19th.

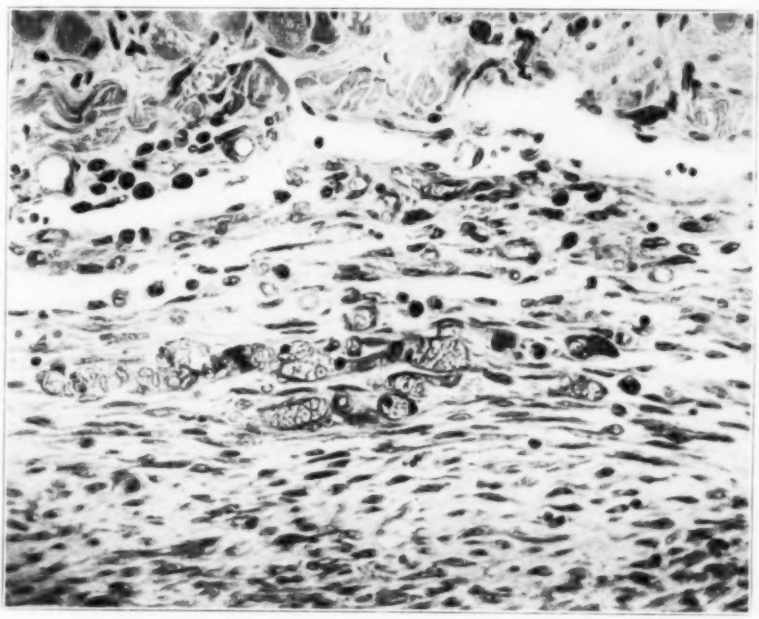

Fig. 23.—Rabbit 79. Section shows at one side few fibers of the upper layer of the myocardium. Rest of section composed of very much thickened, cellular vascular pericardium. Magnification 185 diameters.

Autopsy.—No edema. Heart weight 7.3 gm. Kidneys, weight 16.9 gm., capsule strips easily. On section pin-point hemorrhagic spots seen in cortex. Microscopically the glomeruli are much congested and appear larger than normal, because vessels are full of blood. Otherwise normal.

PROTOCOL 245.—Rabbit. Weight 2050. Caged January 3. On 4th given 0.0125 gm. potassium bichromate. Repeated January 25, Feb. 10, March 3 Died March 11.

Autopsy.—No edema. Microscopically the kidneys show the characteristic increase in connective tissue situated for the most part near the periphery and

often entirely replacing the tubular structure. There are also a few dilated tubules.

PROTOCOL 257.—Rabbit. Weight 2330. Caged January 7. On 8th given 21 minims potassium bichromate, 1 per cent. Repeated on 27, February 10, March 3. Found dead April 13.

Autopsy.—No edema. Slight acute fibrinous pericarditis. Heart weight 6.35 gm. Kidneys, weight 10.8 gm., macroscopically capsule strips easily, surface very irregular with many deep depressions.. On section bands of connective tissue can be seen running down from the depression into the substance of organ. Microscopically in the areas beneath the depressions are bands of connective tissue which have almost entirely replaced the tubules, though the glomeruli still remain. There is some increase in lymphoid cells, but no dilatation of tubules.

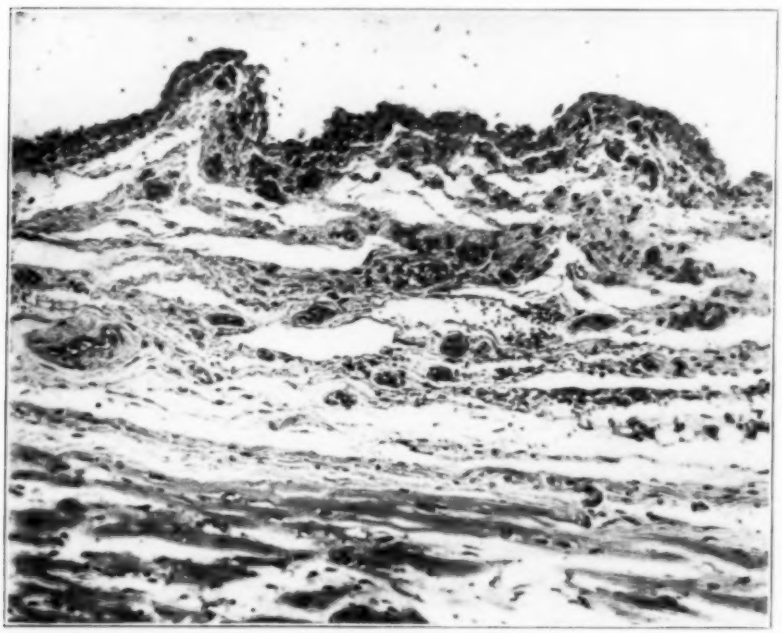

Fig. 24.—Rabbit 266. Section shows much thickened cellular vascular pericardium with papular surface. Magnification 100 diameters.

PROTOCOL 264.—Rabbit. Weight 2100. Caged January 31. February 13 given 0.002 gm. uranium nitrate. Repeated every three days up to March 28. Killed April 30.

Functional Test.—Twenty-four per cent. of phenolsulphonephthalein excreted in one hour.

Autopsy.—Slight amount of free fluid in all cavities. Heart weight 4.3 gm. Kidneys, weight 12 gm., macroscopically normal. Capsule strips easily. Some small areas of round-cell infiltration scattered through this section. Very marked increase in the connective tissue, often in long bands running from periphery down into medulla or scattered in smaller areas irregularly through the cortex. In the connective tissue there are a few moderately dilated tubules.

222 Marlborough Street.

STUDY VI. STUDY OF THE WEIGHTS OF KIDNEYS AND HEARTS IN NORMAL RABBITS AND IN THOSE WITH EXPERIMENTAL CHRONIC NEPHRITIS *

R. M. SMITH, M.D., BOSTON

In the course of the study of animals with experimental nephritis it has been possible to collect a considerable amount of material concerning the comparative weights of the heart and kidneys in rabbits. There were available also in the laboratory many data on normal rabbits, which served as a standard of weights. The observations seem sufficiently interesting to record.

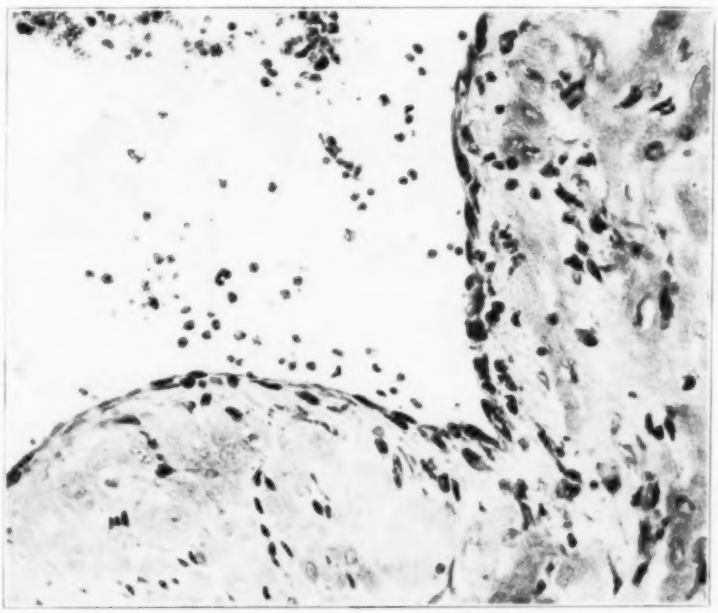

Fig. 25.—Rabbit 268. Section shows a portion of myocardium with overlying endocardium. Endocardium shows proliferation of the endothelial cells with slight edema of the endocardial layer. Magnification 185 diameters.

Grober[5] reports from a study of cardiac hypertrophy in relation to exercise that in caged rabbits the proportion of the body-weight to the weight of the heart is as 1 is to 0.0024. This figure corresponds very closely with that of our normal rabbits; therefore it is taken as the

*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

5. Grober: Untersuchungen zur Arbeitshypertrophie des Herzens, Deutsch. Arch. f. klin. Med., 1907, xci, 502.

standard. No figures could be found in regard to the ratio of body-weight to the weight of the kidneys—our own weights vary considerably—but the great majority are between 1 to 0.0055 and 0.0075, the average of twenty-five rabbits was 0.0066. This makes the relation of the weight of the heart to the weight of the kidneys as 1 is to 2.75.

In some instances it was somewhat difficult to determine the exact weight of the animals. Often during experimentation an animal lost weight markedly, so that at the time of death its body weight was obviously less than it should be. Also, some of the female rabbits were pregnant, and this of course increased their weight. In most instances the weight of the animal at the beginning of the experiment was taken as the correct body-weight. Only marked variations from the normal in heart and kidneys were considered as pathological. If the weights seemed somewhat abnormal but the proportion of heart to kidney was not disturbed no account was made of the variations.

TABLE 1.—TWENTY-FIVE NORMAL RABBITS

No.	Wt. of Animal	Wt. of Heart	Wt. of Kidneys	Wt. of Animal to Wt. of Heart as 1 is to	Wt. of Animal to Wt. of Kidneys as 1 is to	Wt. of Heart to Wt. of Kidneys as 1 is to
1	1320	3.2	9.67	.00242	.00732	....
2	1310	3.3	9.75	.00252	.00744	....
3	1300	3.1	9.7	.00238	.00746	....
4	1290	2.94	8.64	.00228	.00670	....
5	1380	3.15	10.5	.00228	.00760	....
6	1335	2.5	9.0	.00187	.00674	....
7	1350	2.8	8.4	.00207	.00622	....
8	1350	2.95	7.74	.00218	.00573	....
9	1365	4.84	8.75	.00354	.00641	....
10	1320	2.52	9.44	.00190	.00715	....
11	1250	2.3	6.7	.00184	.00536	....
12	1175	2.25	6.9	.00191	.00587	....
13	1130	2.8	8.4	.00247	.00743	....
14	1120	2.7	8.2	.00241	.00732	....
15	1180	2.3	7.3	.00194	.00610	....
16	1070	2.87	8.5	.00268	.00794	....
17	1150	2.3	8.1	.00200	.00704	....
18	1410	3.35	9.35	.00237	.00677	....
19	1120	3.9	8.7	.00348	.00777	....
20	1270	3.4	7.6	.00267	.00600	....
21	1300	3.4	6.4	.00261	.00492	....
22	1240	3.6	6.9	.00290	.00536	....
23	1250	2.9	7.5	.00232	.00600	....
24	1400	4.	9.75	.00285	.00696	....
25	2200	6.4	15.2	.00294	.00691	....
Average	....	....	....	.0024	.0066	2.75

A study of the kidney sections from the organs whose weight showed a variation from the normal did not establish any definite basis for this change. The same was true of those animals in which there was cardiac hypertrophy. These animals showed no greater round-cell infiltration,

connective tissue formation or dilatation of tubules of the kidney than those of the same groups with normal weights.

TABLE 2.—URANIUM SERIES

No.	Wt. of Animal	Wt. of Heart	Wt. of Kidneys	Wt. of Animal to Wt. of Heart as 1 is to	Wt. of Animal to Wt. of Kidneys as 1 is to	Wt. of Heart to Wt. of Kidneys as 1 is to
130	2250	5.	10.2	.00222	.0045	2.04
221	1460	4.4	11.6	.0030	.0080	2.63
189	1400	5.5	12.9	.0039	.0090	2.34
195	1200	3.5	12.1	.0029	.010	3.45
207	1530	4.2	9.6	.00261	.00626	2.28
192	1470	3.4	8.	.00231	.00544	2.35
264	2100	4.3	12.	.00204	.00571	2.79
196	1200	4.5	13.	.00375	.0108	2.88
194	1300	3.5	10.	.0027	.0076	2.85
247	1430	4.6	11.7	.0032	.0081	2.54
261	1760	4.3	10.8	.0024	.0061	2.51
227	1350	3.6	8.1	.0026	.006	2.25
252	2500	6.6	15.7	.0026	.0062	2.38
197	1200	3.7	8.3	.0030	.0069	2.24
250	2400	5.8	12.7	.0024	.0053	2.17
124	1870	5.75	11.55	.00306	.0061	2.00
129	1520	3.8	7.2	.0025	.0047	1.89
208	1740	6.42	11.95	.0037	.0069	1.89
209	....	5.65	11.00	.....	.....	1.94
260	1575	4.65	7.75	.0029	.0049	1.66
190	1390	3.31	12.85	.0023	.0092	3.89
249	2080	5.1	11.5	.0024	.0056	2.25
248	1720	4.2	9.52	.0024	.0055	2.26
177	1250	3.91	11.75	.0031	.0094	3.0
178	1580	4.8	11.8	.0030	.0074	2.46
187	1360	2.9	7.2	.0021	.0053	2.47
193	2500	8.4	14.9	.0033	.0059	1.77

TABLE 3.—CHROMATE SERIES

No.	Wt. of Animal	Wt. of Heart	Wt. of Kidneys	Wt. of Animal to Wt. of Heart as 1 is to	Wt. of Animal to Wt. of Kidneys as 1 is to	Wt. of Heart to Wt. of Kidneys as 1 is to
134	1850	4.1	12.9	.0022	.007	3.14
135	1900	5.0	8.7	.0026	.0046	1.74
231	1330	4.	10.8	.003	.0081	2.7
244	2400	5.7	14.8	.0023	.0061	2.6
263	2000	3.9	9.1	.0019	.0045	2.33
262	1550	9.5	14.8	.0029	.0095	3.29
257	2330	6.35	10.8	.00272	.00463	1.70
222	1300	6.1	17.	.0047	.013	2.78
223	1530	4.7	11.7	.0030	.0076	2.49
224	1730	5.	14.5	.0028	.0083	2.90
225	1700	5.7	12.5	.0033	.0073	2.15
258	3310	8.7	16.	.0026	.0048	1.83
228	1310	4.3	12.8	.0032	.0097	2.97

The study of the charts, however, shows some interesting facts. Of the animals having lesions produced by uranium nitrate and potassium bichromate taken together 39.4 per cent. showed some variations from normal of the weights of heart and kidneys. The smallest percentage was

in those having uranium nitrate in large doses every three weeks, but histologically, they showed as a group very marked lesions. Over one-half of those showing variations, eight in number, or 21.5 per cent., showed a small kidney, one-half of them associated with cardiac hypertrophy.

TABLE 4.—FOWLER'S SOLUTION SERIES

No.	Wt. of Animal	Wt. of Heart	Wt. of Kidneys	Wt. of Animal to Wt. of Heart as 1 is to	Wt. of Animal to Wt. of Kidneys as 1 is to	Wt. of Heart to Wt. of Kidneys as 1 is to
237	1950	5.8	14.5	.003	.0073	2.50
236	1920	5.35	17.2	.0027	.009	3.21
235	2500	6.8	18.7	.0027	.0075	2.75
239	2250	5.1	14.6	.0022	.0065	2.86
243	2280	7.3	16.9	.0032	.0074	2.31
234	2470	4.86	11.9	.0019	.0048	2.45
238	1730	5.55	11.15	.0032	.0064	2.
253	2250	5.5	11.	.0024	.0049	2.
255	2180	5.1	15.8	.0023	.0072	3.
254	1950	5.15	12.1	.0026	.0062	2.26

TABLE 5.—ANIMALS RUNNING OVER 3 MONTHS

	No. with Wts. Recorded	Variation in Weights	Small Kidneys Normal Heart	Normal Kidneys Large Heart	Small Kidneys Large Heart	Large Kidneys.
Uran. 0.002 gm. every 3 days...	11	6=54.5%	2	2	2	0
Uran. 0.005 gm. every 3 weeks..	15	3=20 %	0	0	1	2
Pot. Bichrom. 0.0125 gm. every 3 weeks	12	6=50 %	2	1	1	2
Uran. and Bichrom. together ..	..	15	4	3	4	4
	38	39.4%	10.5%	7.9%	10.5%	10.5%
Fowler's sol. 8-10 m. every 3 weeks	8	4=50 %	1	1	0	2
Total	46	19	5	4	4	6

TABLE 6.—FUNCTION AND EDEMA TESTS IN ANIMALS WITH ABNORMAL WEIGHTS

	No.	Functional Test Tried	Functional Test Delay	Edema Test Tried	Edema Test Present
Animal with small kidney, normal heart..	5	3	3	5	0
Normal kidney, large heart	4	3	2	4	3
Small kidney, large heart	4	2	1	5	2
Large kidney	6	5	1	5	0

The animals with small kidneys and normal hearts in which the functional test was tried, all showed delayed excretion, but none of them had edema. Three out of four of those with heart hypertrophy in addition showed edema. Those with large kidneys showed, with one exception, normal excretion and no edema.

Further observations in a larger number of animals are necessary before definite conclusions can be drawn.

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STUDY VII. PRODUCTION OF EDEMA IN EXPERIMENTAL CHRONIC NEPHRITIS *

R. M. SMITH, M.D., BOSTON

Among the problems connected with the study of experimental nephritis, is the question of the formation of edema and the relation, if any, which it bears to the renal lesion. There seems to be a rather general belief, supported by certain experimental work, that injury to the tubules

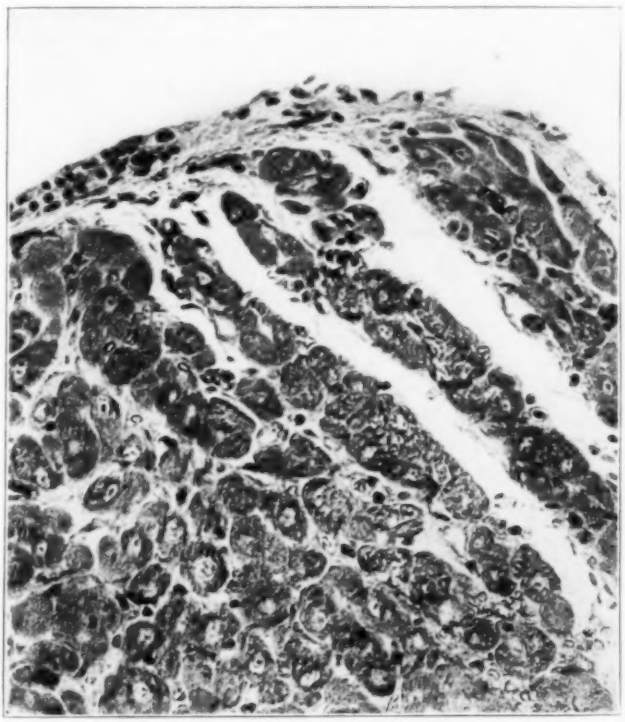

Fig. 26.—Rabbit 279. Section shows portion of endocardium with moderate cellular infiltration. Myocardium shows cellular infiltration. Magnification 185 diameters.

of the kidney alone will not cause edema, but that there must be in addition some lesion of the vascular system. What part sodium chlorid plays in the production of edema has also been studied by many investi-

*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

gators. In acute nephritis, produced by uranium nitrate and rarely by potassium bichromate, edema occurs without the addition of salt to the diet or without the administration of both salt and water in excess. This does not occur, however, in chronic nephritis in rabbits, except very rarely, and not at all in the series of animals in this laboratory.

The following experiment was carried out to see if any further light could be thrown on this subject. All the animals used for experiment had received toxic substances extending over a period in excess of three months; most of them had had no injections for several weeks, and thus did not have an acute lesion. A detailed description of the production of the lesion together with the macroscopic and microscopic appearance of

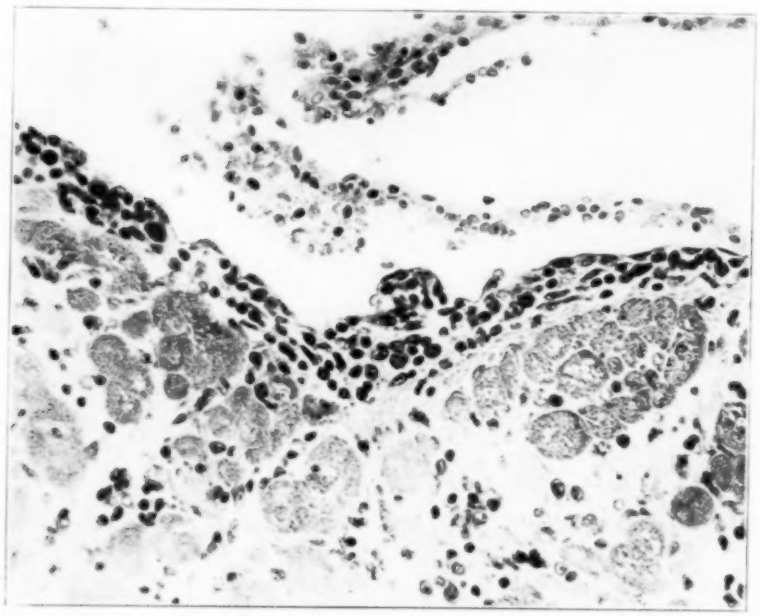

Fig. 27.—Rabbit 79. Section shows quite cellular endocardium with moderately cellular underlying myocardium. Magnification 185 diameters.

the kidneys will be found in another paper. The animals were given 100 c.c. of a 3 per cent. sodium chlorid solution by stomach-tube daily for a period of from four to six days and then killed. Thirty-five animals were thus treated and at autopsy nine showed edema of varying degrees.

The animals used for experimentation had lesions produced as follows:

Uranium Nitrate 0.002 gm. every third day	= 8
Uranium Nitrate 0.005 gm. every three weeks	=11
Potassium Bichromate 0.0125 gm. every three weeks	=10
Fowler's solution 8-10 m. every three weeks	= 6
	35

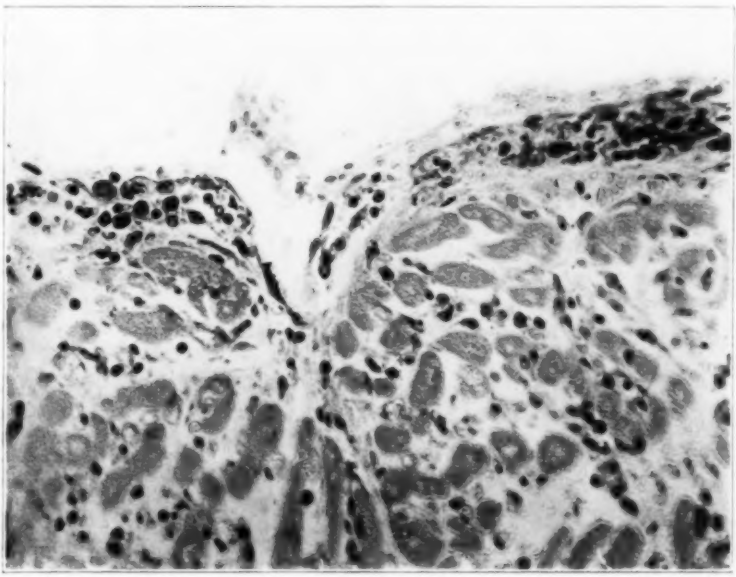

Fig. 28.—Rabbit 79. Section shows quite cellular endocardium with moderately cellular underlying myocardium. Magnification 185 diameters.

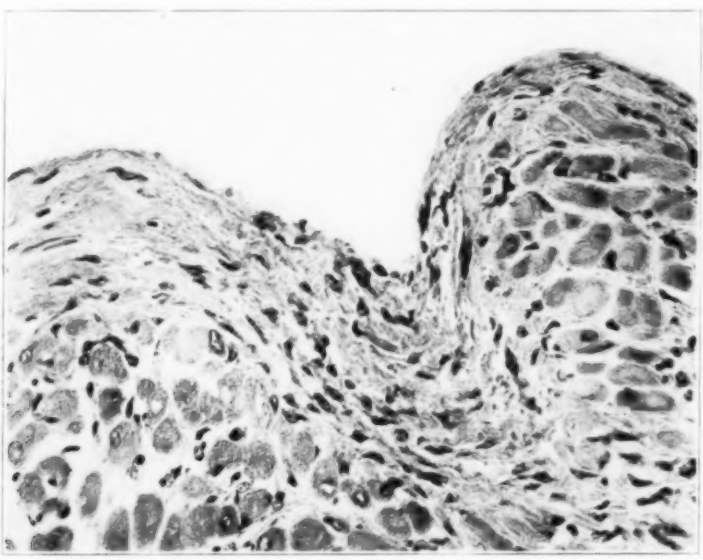

Fig. 29.—Rabbit 266. Section shows a portion of myocardium with a thickened endocardial layer. Magnification 185 diameters.

The nine showing edema were thus distributed:

Uranium Nitrate 0.002 gm. every third day	= 6
Uranium Nitrate 0.005 gm. every three weeks	= 2
Potassium Bichromate 0.0125 gm. every three weeks	= 1
	9

Histologically the kidneys of the animals showing edema were not different from those of the same group in which no edema developed. The lesions were of the same character and of no greater or no less degree.

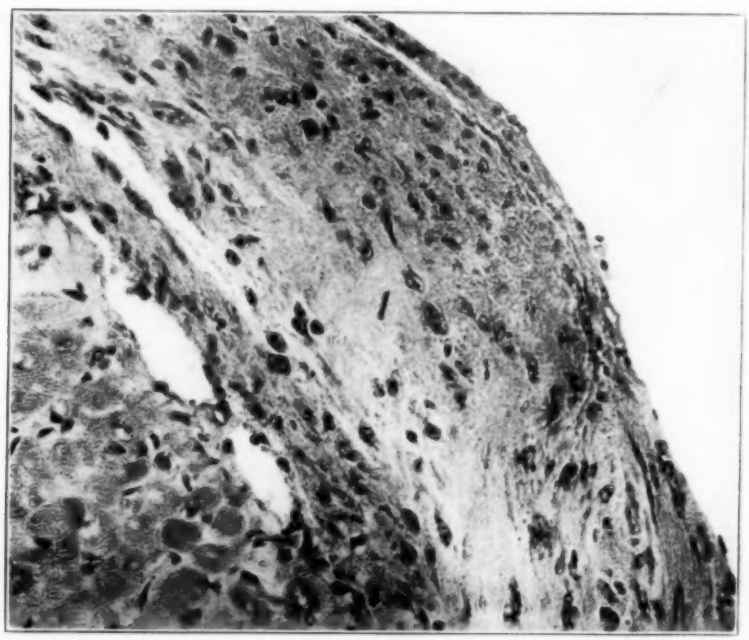

Fig. 30.—Rabbit 266. Section shows a small bit of the myocardium with a very much thickened, somewhat cellular endocardium. Magnification 185 diameters.

It seems then that the cause of the edema must be sought elsewhere than in histological variations from the normal.

The animals were weighed at the beginning of the experiment and each day after that before the salt solution was given. Of those not showing edema at autopsy, twenty-six in number, there was a gain in weight in twelve, a loss of weight in nine, no change of weight in five.

In those showing edema at autopsy, nine in all, there was a gain in weight in four, a loss of weight in four, no change of weight in one.

Therefore, a weight chart is no indication of the appearance of edema in rabbits experimented on in this way.

In the first animals used the daily amount of urine excreted was measured, but no constant or marked variation in the output could be found and the procedure was therefore given up as being of no value in this connection.

These same animals were also subjected to the functional test with phenolsulphonephthalein. Though this matter is reported in another paper the results are interesting from this different point of view. Of the eight animals having uranium 0.002 gm. every third day, and showing

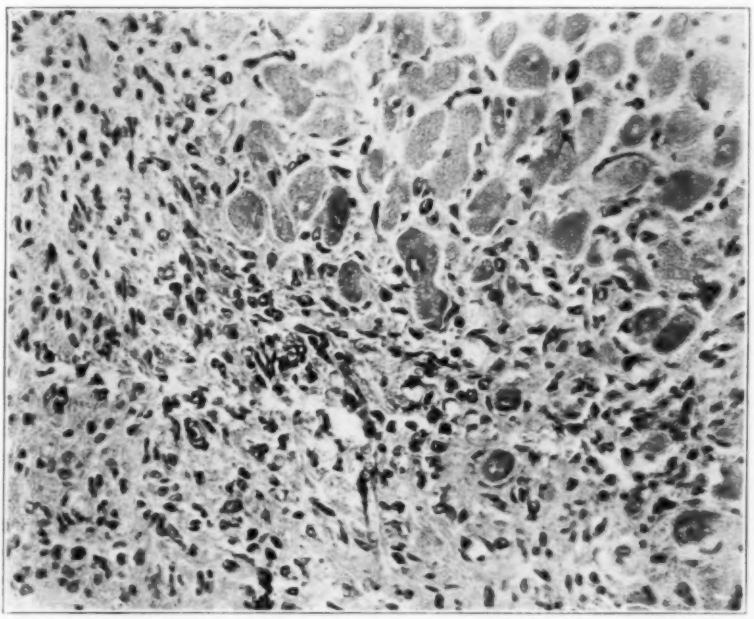

Fig. 31.—Rabbit 266. Section shows a portion of myocardium very largely replaced by cellular connective tissue. This connective tissue was continuous with the connective tissue of the endocardium.

edema, five were tested with phenolsulphonephthalein, and four showed delayed excretion. Of the animals having uranium nitrate 0.005 gm. every three weeks and showing edema, two in number, the test was tried in one and the excretion was normal. The test was not tried in the rabbit having edema with a bichromate lesion. This would perhaps indicate a functional injury to the kidney cells which would not allow the normal excretion of either water or some other substance. The relative weights of heart and kidney to the body-weight is also interesting in this connec-

tion. Of the first uranium group of animals showing edema, six in number, two had small kidneys, four had enlarged hearts.

In the second uranium group, two in number, the heart and kidney weights were normal. The one animal with edema in the bichromate series had an enlarged heart. The number of animals here is too small for any definite conclusions, but it is suggestive that of the nine animals having edema, five had cardiac hypertrophy and only two, small kindeys.

These facts are collected in Table 7.

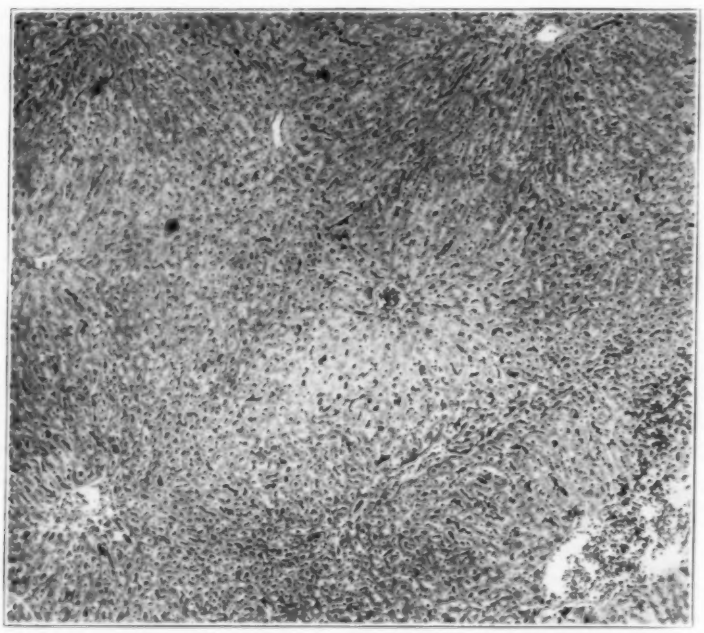

Fig. 32.—Rabbit 273. Liver shows acute congestion of the sinusoids. Magnification 125 diameters.

TABLE 7.—EDEMA EXPERIMENTS

	Test Tried	Edema Present	Phenol-sul. Test Tried	Excretion Delayed	Small Kidney	Large Heart
Uran. 0.002 gm. every 3 days	8	6	5	4	2	4
Uran. 0.005 gm. every 3 wks.	11	2	1	0	0	0
Bichrom. 0.0125 gm. every 3 wks.	10	1	0	..	0	1
Fowler's 8-10 m. every 3 wks.	6	0	..	..	..	..
Total	35	9	6	4	2	5

From these experiments we may draw the following conclusions:

1. Edema may be produced in animals having experimental chronic kidney lesions by the administration of sodium chlorid and water.

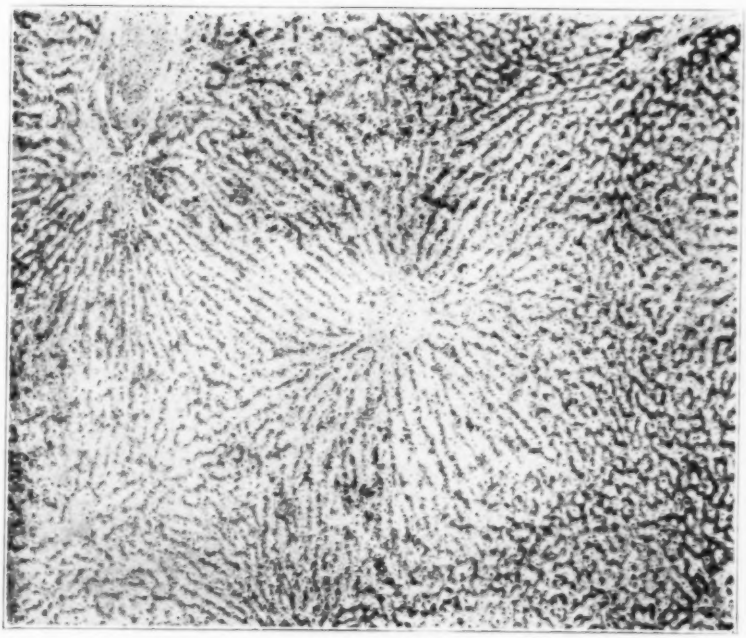

Fig. 33.—Rabbit 266. Liver shows distinct dilatation of the sinusoids, particularly those radiating out from the central vein in the center of the picture with atrophy of the hepatic cells. Magnification 125 diameters.

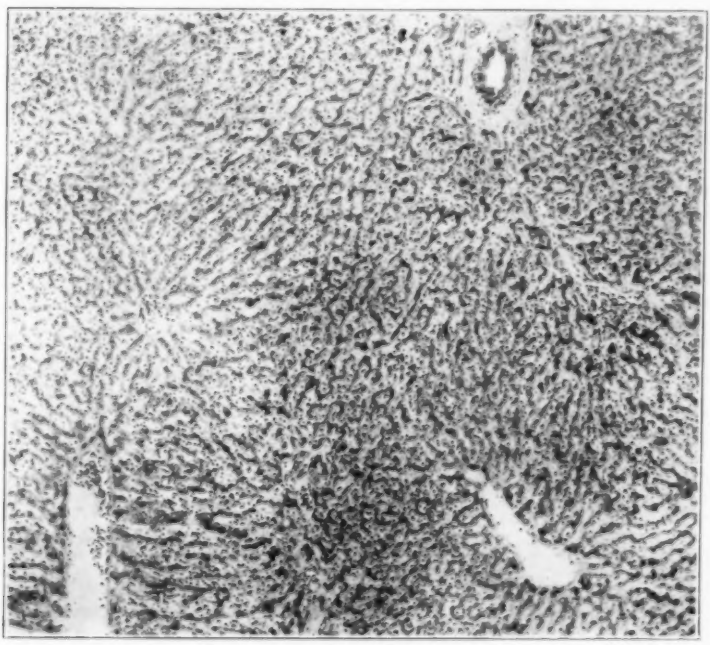

Fig. 34.—Rabbit 282. Liver shows fairly marked dilatation and congestion of the sinusoids. Magnification 125 diameters.

2. The occurrence of edema does not appear to bear any direct relation to the severity or character of the lesion of the kidney as shown by histological study.

3. The weight of the animals during experimentation does not serve as a reliable guide for the appearance or non-appearance of edema.

4. The amount of urine excreted gives no aid in the study of edema formation.

5. Functional tests in animals showing edema would suggest the possibility of some damage to excretory function of cells.

This matter requires further study.

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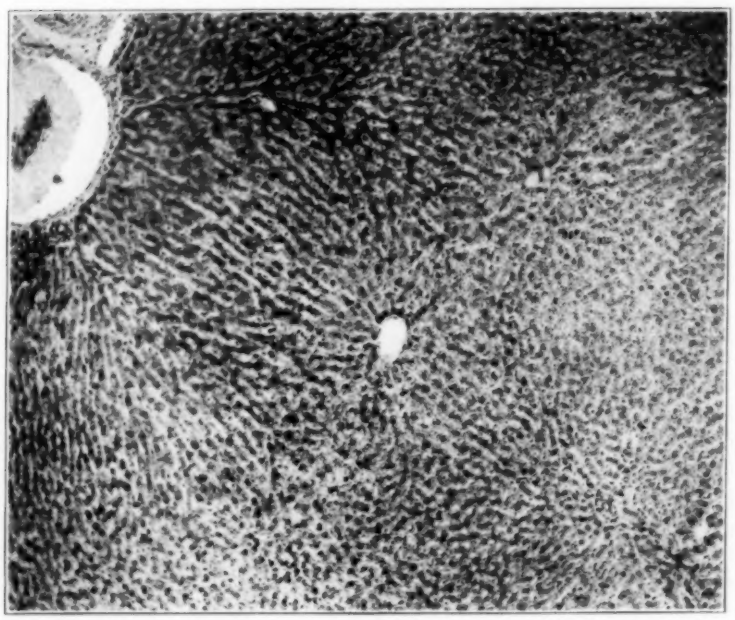

Fig. 35.—Rabbit 268. Liver shows very slight change and may be taken as a fairly normal liver. Magnification 125 diameters.

STUDY VIII. A RENAL FUNCTION TEST (PHENOLSULPHONEPHTHALEIN) IN ANIMALS WITH EXPERIMENTAL CHRONIC NEPHRITIS *

R. M. SMITH, M.D., BOSTON

There have been many tests devised to investigate the excretory function of the kidney. The basis of most of them is the time required to

*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

excrete a certain portion or all of a measured amount of a given drug. The most recently tried drug is phenolsulphonephthalein. It has been used by Rowntree and Geraghty[6] to test the excretory power of kidneys in human beings. They say in favor of this drug that it is all excreted by the kidney, that the drug undergoes no chemical change in the body, and that it is excreted quickly. It is stated that 40 to 60 per cent. of the amount given is excreted in normal individuals within one hour after it first appears in the urine.

Experiments were tried with this drug in animals having chronic kidney lesions produced by injection of uranium nitrate, potassium

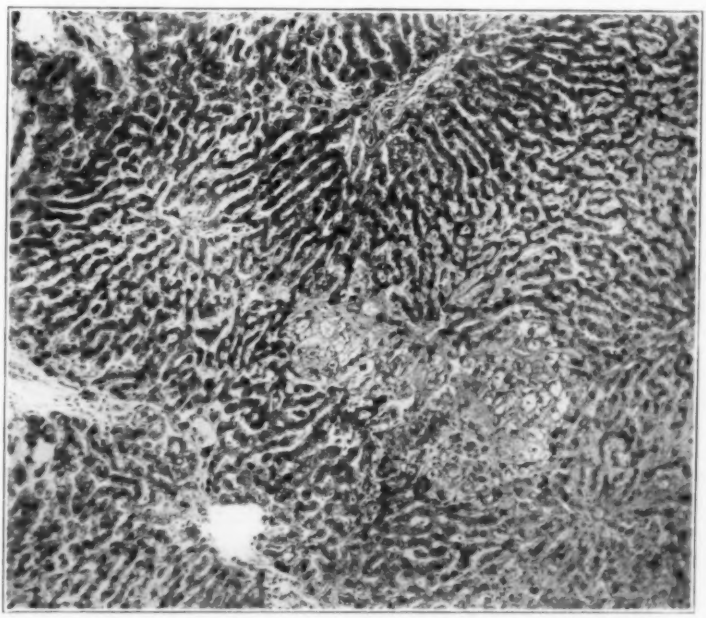

Fig. 36.—Rabbit 79. Liver shows irregular areas of almost complete disappearance of liver cells and their place taken by very large dilated sinusoids or lakes of blood. Magnification 125 diameters.

bichromate and arsenic. The details of the production of the lesion have been described fully in another paper. The functional tests were carried on in the following manner:

One milligram of phenolsulphonephthalein in watery solution was injected subcutaneously. Male rabbits were used at first, so that catheterization was easy. They were catheterized immediately following the injec-

6. Rowntree and Geraghty: Jour. Pharm. and Exper. Therap., 1909-1910, i, 579.

tion, and the urine was allowed to flow into a bottle which contained a few drops of strong sodium hydrate solution. As soon as any of the drug appeared in the urine it could be detected by the pink color which it is well known alkaline solutions of phenolsulphonephthalein assume. The time was then recorded and the catheter withdrawn. At the end of one hour the catheter was again inserted and all the urine in the bladder collected. The bladder was then washed out once with water and the wash-water added to the collected urine. This was then made strongly alkaline with sodium hydrate, and diluted to 50 c.c. with water. This of course gave a solution with a depth of color dependent on the amount

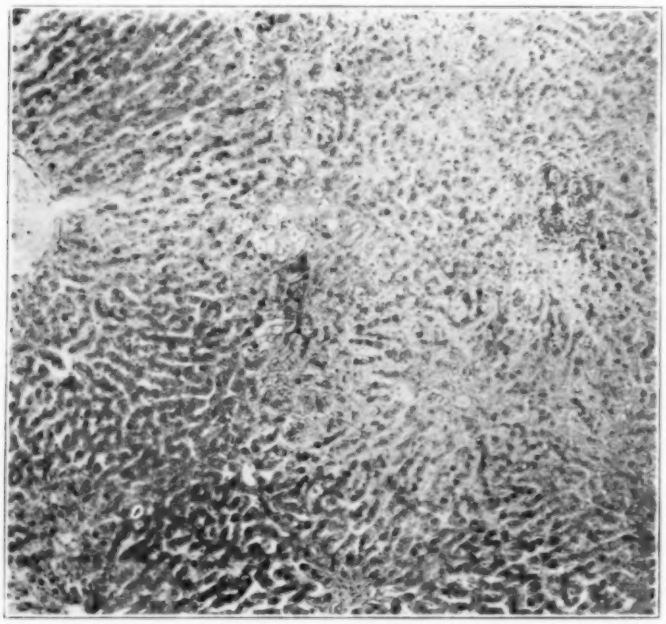

Fig. 37.—Rabbit 79. Liver shows irregular areas of almost complete disappearance of liver cells and their place taken by very large dilated sinusoids or lakes of blood. Magnification 125 diameters.

of phenolsulphonephthalein it contained. To determine the amount of this a standard solution of phenolsulphonephthalein was prepared containing a measured amount in 50 c.c. of fluid (water and urine). For a portion of the diluent of the standard solution urine was used, otherwise the colors were not exactly the same in the control and the test as the solution to be tested contained the yellow coloring-matter found in rabbit's urine. A portion of the standard solution and of the urine containing the unknown amount of the drug were placed in the two tubes

of a Dubosc q colorimeter and the comparison made. Having thus determined the amount of phenolsulphonephthalein excreted in one hour, the percentage of the amount given was easily calculated.

From observations on a good many rabbits it was found that the phenolsulphonephthalein appeared in the urine in about twenty minutes from the time it was given subcutaneously. The time variations from this in either direction were small. Since it was not possible to catheterize the female rabbits the drug was given subcutaneously, and the animal killed in one hour and twenty minutes. The urine in the bladder was then collected and the estimation made as before. This gave a fairly accurate estimate of the per cent. excreted.

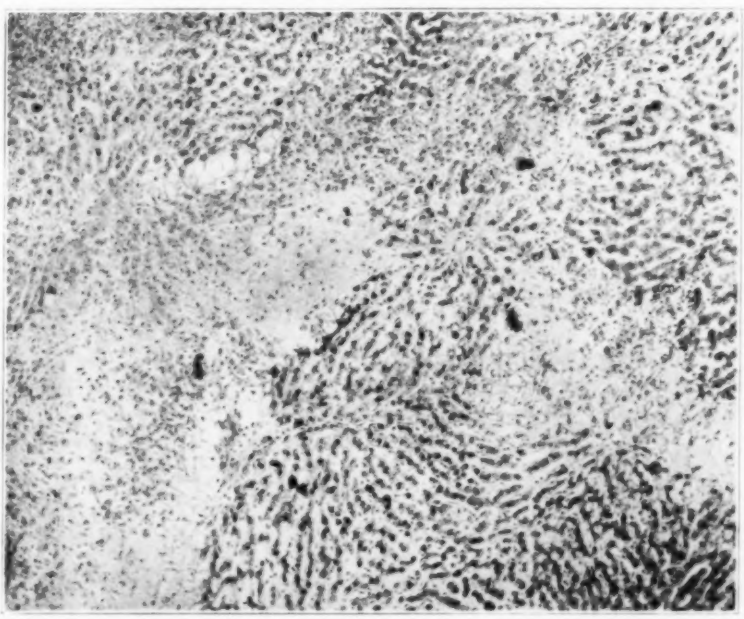

Fig. 38.—Rabbit 79. Liver shows irregular areas of almost complete disappearance of liver cells and their place taken by very large dilated sinusoids or lakes of blood. Magnification 125 diameters.

In the great majority of cases tested, over 40 per cent. of the drug was excreted in one hour, which conforms to the statement quoted at the beginning of the discussion. In a few normal rabbits tried the excretion was found to be about this per cent. Only considerably less than this was considered a delayed excretion.

Number of animals given the test, 31.
Delayed excretion, 16=51.6 per cent.
Very markedly delayed excretion, 4.

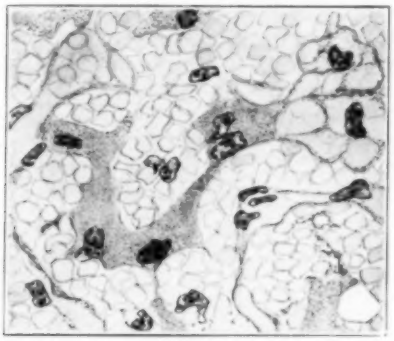

Fig. 39.—Rabbit 79. Shows hemorrhage about liver cells.

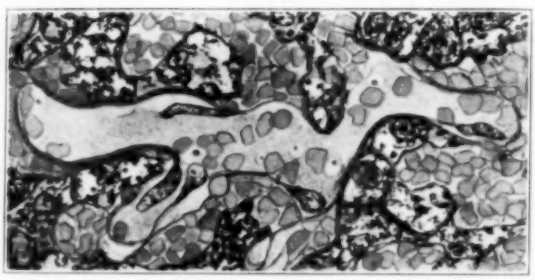

Fig. 40.—Rabbit 79. Shows hemorrhage about liver cells.

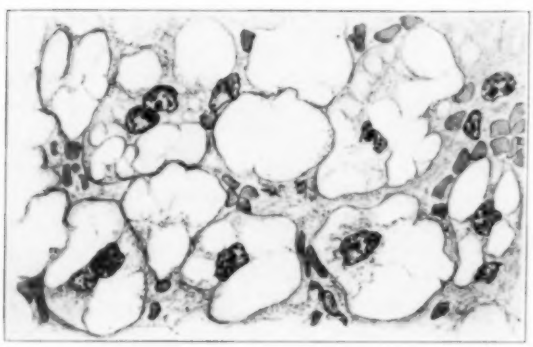

Fig. 41.—Rabbit 79. Shows vacuolar degeneration of liver cells.

The lesions in these animals were produced as shown in Table 8.

TABLE 8.—PRODUCTION OF LESIONS

	Test Tried	Delayed Excretion	Markedly Delayed Excretion
Uranium nitrate 0.002 gm. every 3d day.	7	5	2
Uranium nitrate 0.005 gm. every 3 wks.	10	4	0
Potassium bichromate 0.0125 gm. every 3 weeks.	9	4	1
Fowler's solution m. 8-10 every 3 weeks.	5	3	1
Total	31	16	4

Here, as in the other experiments, it was impossible to see any definite relation between the delayed excretion of the drug and the histological lesions in the kidney. That is, the animals of the same groups as these showing delayed excretion, but in whom excretion was normal, had lesions as marked or even more so than those in which it was delayed. It is interesting that some of the animals that had Fowler's solution showed delayed excretion with little visible change in kidney.

It might be interesting again to compare from this new point of view the edema test and the organ weights in these animals.

Of the sixteen rabbits with delayed excretion:

1. Edema test tried on	16
Edema present at autopsy	4
2. Organs weighed in	16
Variation from normal	7
Small kidney, normal heart	3
Small kidney, large heart	1
Normal kidney, large heart	2
Large kidney, large heart	1

Of the four with very markedly delayed excretion:

1. Edema test tried	4
Edema present	2
2. Organs weighed in	4
Variation from normal	3
Small kidney, large heart	1
Normal kidney, large heart	1
Large kidney, normal heart	1

The small number of animals experimented on makes dogmatic conclusions impossible, but it is certain from the work thus far presented that the functional capacity of the kidney evidenced in secretion of water and certain drugs cannot be estimated by histological examinations; that kidneys with the most marked histological lesions frequently have normal function, and others with apparently identical or even lesser lesions showed marked disturbance.

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STUDY IX. THE EFFECT OF SPARTEIN AND ADRENALIN (EPINEPHRIN) INJECTIONS ON THE KIDNEY OF THE RABBIT *

B. M. SMITH, M.D., BOSTON

Walker and Christian have described the production of cardiac lesions — myocarditis, pericarditis, endocarditis — in rabbits by the injection of spartein sulphate (0.01 to 0.04 gm.) and adrenalin (epinephrin) chlorid (0.1 to 0.2 c.c. of a 1-1,000 solution). In some animals the spartein was given subcutaneously and the adrenalin intravenously, but in most, both drugs were injected intravenously. I have examined the kidneys from twenty-nine of these animals.

Macroscopically the kidneys did not show any departure from the normal except in occasional instances when they appeared injected. This injection did not bear any apparent relation to the cardiac condition, but was evidently independent of it. Microscopically no lesions were found which in any way could be associated with the injection of the drugs. A few of the animals showed some spontaneous lesions as I have mentioned in connection with studies on the kidneys of rabbits which received uranium nitrate and other kidney irritants. These spontaneous lesions occurred in rabbits autopsied from one hour to two or three days after the injection of spartein—much too soon for any causal relation to exist between the drug and the histological finding in the kidney. The chronic lesions consisted of a slight connective tissue increase—in one or two instances with some dilatation of the renal tubules.

Nearly all the sections showed a marked injection of the vessels, especially those of the glomeruli and medulla. Sometimes only the vessels going in from the cortex were markedly congested. In some of the kidney this condition was extreme, making the whole section appear very red under the microscope. In no case, however, was it possible to find any evidence of the breaking through of the blood into the spaces without the vessels. Apparently simply an unusual amount of blood was present in the vessels at the time of death. An attempt was made to match up the more bloody sections with the more severe cardiac conditions, but no constant relationship was found. In some instances, however, the kidney sections of animals dying in convulsions were greatly injected, but even this was not an unfailing condition.

No tests of kidney functions were made with these animals.

So far as this study goes it supports the statement made by Fleisher and Loeb[7] that injections of spartein and adrenalin cause no lesions in the kidney.

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*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

7. Fleisher and Loeb: Further Investigations in Experimental Myocarditis, THE ARCHIVES INT. MED., 1910, vi, 427.

STUDY X. EXPERIMENTAL MYOCARDITIS PRODUCED BY SPARTEIN SULPHATE AND ADRENALIN CHLORID *

I. CHANDLER WALKER, M.D., BOSTON

Many observers have produced lesions of the myocardium in various ways; by the intravenous injections of cultures of *Staphylococcus pyogenes aureus* (Ribbert[8]), diphtheria bacilli (Babes[9]), diphtheria toxin (Charrin,[10] Welch and Flexner,[11] Mollard and Regaud,[12] and Flexner[13]), cultures of streptococci (Tallquist[24]), by ligation of coronary vessels (Baumgarten[15]), by exposing animals to high temperature (Zwaschkewitsch,[16] Litten,[17] Naunyn,[18] Nasaroff,[19] Werhovsky,[20] Welch[21]), by injections of adrenalin chlorid (K. Ziegler,[22] Pearce,[23] Gröber,[24] Miesowicz[25]), and by injections of spartein and adrenalin (Fleisher and Loeb[26]). The more acute lesions of the myocardium have been the ones chiefly studied by these experimenters. For the production of chronic lesions the method used by Fleisher and Loeb seems to be the most satisfactory, and has been used in the experiments here reported, which were carried on in the laboratory of the Theory and Practice of Physic in the Medical School of Harvard University at the suggestion and under the supervision of Dr. H. A. Christian.

Rabbits were the only animals used in these experiments, and for convenience they may be grouped into five series in which the spartein

*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

8. Ribbert: Fortsch. d. Med., 1886, iv, 1.
9. Babes: Virchows Arch. f. path. Anat., 1896, cxix, 460.
10. Charrin: Semaine Méd., 1890, x, 285.
11. Welch and Flexner: Bull. Johns Hopkins Hosp., 1891, ii, 107; Bull. Johns Hopkins Hosp., 1892, iii, 17.
12. Mollard and Regaud: Ann. de l'Inst. Past., 1897, xi, 97.
13. Flexner: Johns Hopkins Hosp. Rep., 1897, vi, 259.
14. Tallquist: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1899, xxv, 159.
15. Baumgarten: Am. Jour. Physiol., 1899, ii, 243.
16. Zwaschkewitsch: Dissertation, St. Petersburg, 1870.
17. Litten: Virchows Arch. f. path. Anat., 1887, lxx, 10.
18. Naunyn: Arch. f. exper. Path., 1884, xviii, 49.
19. Nasaroff: Virchows Arch. f. path. Anat., 1882, xc, 482.
20. Werhovsky: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1895, xviii, 72.
21. Welch: Med. News, London, 1888, lii, 365.
22. K. Ziegler: Beitr. z. path. Anat. u. z. allg. Path. (Ziegler's), 1905, xxxviii, 229.
23. Pearce: Jour. Exper. Med., 1906, viii, 400.
24. Grober: Deutsch. med. Wchnschr., 1907, xxxiii, 744.
25. Miesowicz: Wien klin. Wchnschr., 1909, xxii, 79.
26. Fleisher and Loeb: THE ARCHIVES INT. MED., 1909, iii, 78. Jour. Am. Med. Assn., 1909, liii, 1561; THE ARCHIVES INT. MED., 1910, vi, 427. Strickler and Fleisher: Jour. Pharm. and Exper. Therap., 1910, ii, 55.

sulphate and adrenalin chlorid were used by different methods in order to determine the most satisfactory procedure for producing experimental myocarditis.

In the first series, four rabbits were injected intravenously with maximum doses of spartein sulphate,[27] and these injections were not followed by injections of adrenalin chlorid. The animals were injected from once to thirty times at three-day intervals.

In the second series twenty-four young rabbits were injected subcutaneously with spartein sulphate 0.025 gm., followed subcutaneously in three to five minutes by adrenalin chlorid[28] 0.2 c.c. of a 1 to 1,000 solution. These injections were repeated every three days, and a pair of rabbits of approximately the same weight were killed at successive three-day intervals. In addition in this series two other rabbits received injections in the same way as the above every day for a period of six weeks, and then every other day for six weeks.

In the third series were eight rabbits in which spartein sulphate was injected subcutaneously in doses of 0.025 gm., followed intravenously in five to fifteen minutes by adrenalin chlorid 0.2 c.c. of a 1 to 1,000 solution.

In the fourth series six rabbits were injected with spartein sulphate and adrenalin chlorid, both intravenously, in small doses, repeated at three-day intervals, and extending over a long period, one to three months.

The fifth series comprised eleven rabbits injected intravenously with maximum doses of spartein sulphate followed intravenously in five to fifteen minutes by adrenalin chlorid 0.2 c.c. of 1 to 1,000 solution.

The rabbits in all series either died or were killed at varying time intervals after the first injection, and so received a varying number of injections of varying size given in varying combinations.

No animals died from the effect of spartein sulphate when injected subcutaneously, but there were several deaths due to the drug when given intravenously. The animals died with either respiratory paralysis, gasping for breath, or with convulsions, or with both. Death may be avoided by slowly injecting the drug with frequent pauses, thereby allowing a mixture of the drug with the blood in the circulation and much greater doses may be safely used in this way. Some rabbits seem to be more susceptible to spartein than others, since several rabbits of the same weight and age may survive the same injection, while one or two others will not. Only two deaths out of about thirty rabbits used could be considered due to adrenalin chlorid used intravenously, and these had received spartein just previously. The deaths were convulsive with respiratory paralysis. The best lesions were produced by maximum doses of spartein given intravenously (making the animal as weak and stupid as

27. Merck's preparation of spartein sulphate was used throughout.

28. Parke, Davis & Co.'s preparation of adrenalin chlorid was used throughout.

possible and still survive) followed intravenously in a few minutes by adrenalin. Adrenalin given subcutaneously had no effect.

All animals injected intravenously with one or two large doses of spartein followed intravenously by adrenalin at autopsy showed much blood-stained fluid in the pericardial, thoracic and abdominal cavities. A smaller amount of less bloody fluid was found in these cavities when the spartein was used subcutaneously followed by adrenalin intravenously. After two injections the fluid seemed to be absorbed and no further exudation appeared to take place, as none was present in rabbits dying after three or more injections.

The methods used in this experimental work having been briefly described, the various series will now be taken up and the lesions described.

SERIES 1.—Four rabbits injected with spartein sulphate 0.025 gm. intravenously without adrenalin. One rabbit was killed a few minutes after injection, and showed slight congestion. Another was killed four hours after injection and showed marked congestion, and a distinct focus of deeper congestion on surface of left ventricle. A third rabbit was injected every three days for twenty-five injections and another rabbit for thirty injections. Both of these showed simply a congestion of the myocardium. In these two rabbits the spartein was gradually increased until they received 0.05 gm. several times. Thus it is seen that spartein alone, given in twice the amount which with adrenalin will cause a lesion, produces no lesions.

SERIES 2.—Twenty-four rabbits were selected, weighing between 1100 and 1400 gm., paired according to weights and were injected subcutaneously at three-day intervals with spartein sulphate 0.025 gm., followed subcutaneously in three to five minutes with adrenalin chlorid 0.2 c.c. of a 1 to 1,000 solution. Two rabbits were killed three days following the first injection, two more three days after a second injection, and this was repeated until the last two rabbits of this series were killed. Of these twenty-four rabbits, two were discarded after three injections because one of the rabbits contracted an infection. No macroscopic lesions could be observed in any of the rabbits of this series.

Microscopically in three rabbits (No. 167, eight injections, No. 169, nine injections, No. 171, ten injections) there was moderate capillary congestion distinctly in excess of that shown by other animals of the series. In four rabbits (No. 152, one injection, No. 156, three injections, No. 165 and No. 166, seven injections), there was an increased interstitial cellularity. These cells were of the connective tissue type, not uniformly scattered through the myocardium, but occurring in foci. This change was more extensive in the animals receiving the larger number of injections, being very slight in Rabbit 152. A somewhat similar picture (Fig. 3) was presented by an animal (Rabbit 79) of a different series from the ones described in this paper. In two rabbits (No. 159, four injections, No. 163, six injections) there were small foci of young connective tissue. Rabbit 159 showed more of this than Rabbit 163. In none of these rabbits was the lesion extensive, and even where most marked it constituted only a slight departure from the normal.

Two more rabbits were injected subcutaneously with the same dosage as in the preceding series every day for six weeks and then every other day for six additional weeks. One showed no lesion. The other had a large area of old fibrous tissue practically replacing the muscle, with only little shreds of muscle left. These muscle fibers were devoid of nuclei and often took the eosin stain deeply, the cross-striations being lost. This fibrous tissue was very near the

septum at the base of the left ventricle, and it is a question whether it was due to the drugs or whether it was a spontaneous lesion. In its distribution and character it did not resemble a spartein and adrenalin lesion. These protocols will not be given.

It was noted that injecting both spartein and adrenalin at the same site on the same day caused a necrosis and sloughing of the tissues, whereas separated injections on the same day produced no necrosis.

SERIES 3.—Eight rabbits were injected subcutaneously with spartein sulphate 0.025 gm. followed in about ten minutes intravenously by adrenalin chlorid 0.2 c.c., 1-1000 solution. Only four protocols will be given, the others being duplicates.

Rabbit 274 was injected subcutaneously with spartein 0.025 gm. followed intravenously in ten minutes by adrenalin solution[29] 0.2 c.c. This animal died twenty minutes later with respiratory paralysis and convulsions. Microscopically only congestion was present. Rabbit 268, similarly injected at three-day intervals, showed a capillary congestion (Fig. 7) as in Rabbit No. 274.

Rabbit 279, weight 1450 gm., was injected subcutaneously with spartein 0.025 gm., followed intravenously in ten minutes by adrenalin solution 0.2 c.c. Five days later the same was repeated and the rabbit died about ten minutes following this injection. At autopsy there was an increased amount of a straw-colored fluid in all body cavities. Microscopically there was a patchy cellular infiltration throughout the myocardium. In some of these foci many lymphoid cells were present. This was particularly the case in the subpericardial layers. There was also an increased amount of connective tissue about the blood-vessels. Where the round cells showed only a slight increase, the muscle fibers were hypertrophied, showed very marked branching, and an increased number of nuclei, as many as five or six in a line. Where there was considerably increased cellularity (Fig. 4), the muscle was much degenerated, with loss of striations, and in places where the young cells appeared as stellate figures with beginning fibrils, the muscle was atrophied and replaced by new tissue.

Rabbit 277, weight 1480 gm., was injected subcutaneously with spartein 0.025 gm. followed intravenously in ten minutes by adrenalin solution 0.2 c.c., this being repeated every three days for a period of twelve days; thus four injections were given. The rabbit died a few minutes after the last injection. At autopsy considerable free bloody fluid was present in all the cavities, and in addition considerable fibrin in the pericardial cavity, with a slight roughening of the surface of the left ventricle. The heart was large. Microscopically the same general picture was seen as in Rabbit 279, but the process was somewhat more advanced and more extensive. The connective tissue was older, with more fibrils and less cells present, the arterial walls were more thickened, the muscle more extensively atrophied.

Rabbit 284, weight 2200 gm., was injected with spartein sulphate 0.025 gm. followed intravenously in ten minutes by adrenalin solution 0.2 c.c. at four-day intervals over a period of two months, sixteen injections in all. At autopsy no fluid was present, the heart was large and firm. Microscopically a slight increased cellularity diffusely situated was seen, the arterial walls were thickened, and the muscle was hypertrophied.

SERIES 4.—Here six rabbits were used, but as they all showed a similar condition only one protocol will be given. These animals were injected intravenously with small doses of spartein and adrenalin.

Rabbit 282, weight 1920 gm., was injected with spartein sulphate 0.007 gm. followed in about ten minutes by adrenalin solution 0.1 c.c., both intravenously. This was repeated at three-day intervals for seven times, then the spartein was increased to 0.008 gm. and the injections repeated at three-day intervals for seven more times, in all fourteen injections extending over two months' time. At

29. Adrenalin solution whenever used means a 1 to 1,000 solution of adrenalin chlorid.

bloody fluid filled the pericardial cavity. The heart was very large, and left autopsy there was fluid in the abdominal and thoracic cavities, and a muddy auricle and ventricle very firm and thickened, with a white fibrous patch at the base of the left ventricle. Microscopically there was a diffuse increased cellularity of the myocardium with an hypertrophy of muscle fibers, with increased numbers of nuclei, nuclei swollen and nucleoli prominent. The connective tissue about the blood-vessels was thickened. In addition there was a large fibrous patch at the base of the left ventricle entirely replacing the muscle. The other five animals did not show such a fibrous area as described in Rabbit 282, but were duplicates in every other way. The striking change in this series was slight diffuse increased interstitial cellularity, interstitial edema, and moderate connective tissue increase and hypertrophy of muscle (Fig. 2).

SERIES 5.—In this series eleven rabbits were injected intravenously with spartein sulphate and adrenalin chlorid in the following way: Spartein sulphate was injected intravenously in maximum doses, that is as large a dose as the rabbit appeared able to stand. Shortly after such a dose the rabbit would seem very tired with rapid respiration and a rapid, unsteady heart. After an interval of ten to twenty minutes adrenalin solution was injected intravenously with a dose of 0.2 c.c. The adrenalin appeared to produce no marked effect except possibly to accentuate somewhat the already existing symptoms.

One of these rabbits was killed three minutes after the adrenalin chlorid injection, and nothing abnormal was seen.

Another (Rabbit 290) was killed four hours after injection, and at autopsy an area of marked congestion about half a centimeter in diameter, of a bloody red color was situated in the center of the wall of the left ventricle. Microscopically in the animal there was congestion of the subpericardial myocardium as follows: Rabbit 290, weight 1480 gm., injected intravenously with spartein sulphate 0.04 gm., followed in ten minutes intravenously by adrenalin solution 0.2 c.c. The rabbit became very tired and listless, respiration rapid, heart rapid and fluttering, three hours later heart seemed steadier, but animal was very stupid. Four hours after injection the rabbit was killed. Macroscopically there was a bloody red area of congestion on the wall of the left ventricle near the center about 0.5 cm. in diameter. Microscopically there was congestion and edema of the subpericardial myocardium of the left ventricle.

The third rabbit, No. 296, weight 1750 gm., was injected intravenously with spartein sulphate 0.035 gm. followed in ten minutes by adrenalin solution 0.2 c.c. The rabbit seemed very tired after this. It was killed twenty-four hours after injection. At autopsy the thoracic cavity contained much very bloody fluid and the pericardial cavity was filled with bloody fluid. The heart showed areas of congestion of a bright red color on the surface of the right auricle, to a slight extent on the left auricle, and on the surface of the left ventricle an area of dark brownish-red color with slight peripheral congestion. Microscopically in the myocardium of the right and left ventricles there was a very general indistinctness of muscle striations, a diffuse increased interstitial cellularity, and quite a general capillary congestion. In places muscle fibers were markedly degenerated, appearing as deeply staining fibers with very indistinct striation. Some muscle fibers had lost practically all striation. Besides the diffuse cellularity there were very cellular foci in association with markedly degenerated muscle fibers. In places cells have invaded muscle fibers, and hyaline fragments of muscle fibers may be seen scattered among these cells. The cells themselves were not definitely phagocytic, however, for muscle fragments. These cells were of the young connective tissue and endothelial types. Their nuclei were vesicular with fairly fine chromatin granules, and one to three coarser chromatin masses. In some there was a round reddish staining nucleolar mass. The cytoplasm of these cells was very finely granular and usually distinctly basophilic. There was no evident cell membrane. Polynuclear leukocytes play but a small part in the process; a few were found scattered between the muscle fibers, more numerous about the cell foci described above.

A fourth rabbit, No. 293, received intravenously 0.04 gm. spartein sulphate and ten minutes later intravenously 0.2 c.c. adrenalin solution. This animal seemed very tired and quiet after the injection similarly to No. 296, and was killed at the end of thirty-two hours. At autopsy there was a slight amount of a straw-colored fluid in the abdominal cavity, very much and rather bloody fluid in the thorax, while the pericardial cavity was filled with a very bloody fluid, and the pericardial sac seemed to be slightly glued in places to the left ventricle. Areas of fresh hemorrhage were present on the right auricle, much more marked and wide-spread on the left ventricle. Microscopically a very similar picture was seen to that in Rabbit 296. There was evidence of a diffuse degeneration of muscle fibers as in the former. The interstitial cells were more definitely of the connective tissue type with processes and more connective tissue fibrils have been formed. Near the apex of the left ventricle there was a cellular focus of considerable size about much degenerated muscle fibers. Mitotic figures were frequent in this area. In the right ventricle near the auriculoventricular groove there was another focus of cells of young connective tissue type with many polynuclear leukocytes and few plasma cells.

The fifth rabbit, No. 280, weight 1580 gm., was injected with spartein sulphate 0.03 gm., followed in about five minutes by adrenalin solution 0.2 c.c., both drugs given intravenously. After five days the rabbit was killed. At autopsy much free blood-stained fluid was found in the abdominal cavity, with little flakes of fibrin floating on the intestines, still more bloody fluid in the thoracic cavity, and the pericardial cavity was filled with very bloody fluid. A small roughened area was present on the surface of the left ventricle. Microscopically the subpericardial myocardium was very extensively infiltrated with connective tissue, which was moderately cellular. Where there was a larger amount of connective tissue the muscle fibers were much atrophied and evidently numerous fibers had entirely disappeared. From this point the young connective tissue extended deeper into the myocardium interlacing with the muscle bundles. The muscle fibers frequently showed a large perinuclear non-striated area and two or three nuclei were often seen in a fiber. An area of practically normal muscle was present in the center of the wall of the left ventricle, although there was an increased interstitial cellularity. As the endocardium was approached, the connective tissue increased in certain foci and degeneration of the muscle was more extensive.

The sixth rabbit of this series, No. 270, weight 2370 gm., was injected intravenously with spartein sulphate 0.025 gm., followed in fifteen minutes intravenously with adrenalin solution 0.2 c.c. This was repeated three days later and the animal died four days after the second injection, that is seven days after the first injection. At autopsy the abdominal cavity contained 60 c.c. of free blood-stained fluid, the thoracic cavity 18 c.c. and the pericardial cavity was filled with very bloody fluid. The heart muscle was pale. Microscopically there was an increased interstitial cellularity with moderate connective tissue increase.

The seventh rabbit, No. 292, weight 1750 gm., was injected intravenously with 0.03 gm. spartein followed intravenously in fifteen minutes by adrenalin solution 0.2 c.c.; this was repeated two days later and the animal was killed twenty-four hours after the second injection, that is, three days after the first injection. Here larger doses of spartein were given with a shorter interval between. Macroscopically there was an area near the apex on the left ventricle of a brownish color, where the muscle was soft, pale and flabby. Microscopically there was a very great increase of young cellular connective tissue in many places very largely replacing muscle fibers. In other places atrophied and degenerated fibers were scattered in the young connective tissue. Mitoses of connective tissue cells were numerous. This increased cellularity was situated in both walls of the left ventricle throughout the central portion, the base and the apex of the heart being entirely free from pathological change. The whole muscle in the degenerated area was riddled with young connective tissue. Slight congestion was also present.

The remaining rabbits of this series were duplicates of the above, and will not be described. Rabbits receiving such large amounts of spartein would not survive a third injection.

Summary

A total of fifty-seven rabbits were used in these experiments with the following results. A series of four rabbits received intravenously spartein sulphate alone in large doses and showed only congestion of the myocardium. In the second series of twenty-four rabbits receiving spartein sulphate followed by adrenalin chlorid, both subcutaneously, three rabbits showed capillary congestion of the myocardium (Fig. 1) and six showed very slight increased cellularity of the young connective tissue type. Where the change was most marked in this series it constituted only a slight departure from the normal. In addition two other rabbits of this series were injected with the same dosage and in the same manner only daily for six weeks and thereafter every second day for six weeks more; one was negative, and the other had an extensive fibrous area in the myocardium at the base of the left ventricle near the septum. It is uncertain whether the latter lesion was due to the drugs or whether spontaneous; however, it seems more likely to have been spontaneous.

The eight rabbits of the third series were injected subcutaneously with spartein sulphate, 0.025 gm., followed intravenously in about ten minutes by adrenalin solution, 0.2 c.c. At a twenty-five minute interval after injection, congestion of the myocardium was noted; at a five-day interval fluid was found in all the body cavities and microscopically a patchy cellular infiltration of the myocardium as follows: in the subpericardial myocardium were small foci of lymphoid and young connective tissue cells, there was an increased amount of connective tissue about the blood-vessels; and in the myocardium, where there was only slight cellular increase, the muscle showed evidences of hypertrophy; where there was considerable cellular increase, the muscle showed evidences of degeneration. In another rabbit, which received in the same manner four injections extending over a period of twelve days, autopsy showed bloody fluid in all the body cavities, a roughening of the left ventricle and a large heart. Microscopically was noted a similar picture to that seen in the previous rabbit, only more extensive and more advanced. The last rabbit of this series was injected like the above rabbits for sixteen times, extending over a period of two months, and this rabbit showed a diffuse increased cellularity, thickened arterial walls and muscle hypertrophy. In the fourth series of six rabbits injected with spartein sulphate in small doses followed in ten to twenty minutes by adrenalin solution, 0.2. c.c., both drugs given intravenously, all showed a similar lesion. At autopsy there was fluid in all body cavities and blood in the pericardial cavity, several showed also macroscopically a lesion of the left heart. Micro-

scopically there was a diffuse increased cellularity of the myocardium with an hypertrophy of the muscle and thickened walls of the blood-vessels. In addition one rabbit showed a large fibrous patch at the base of the left ventricle entirely replacing the muscle. In the last series eleven rabbits were injected intravenously with maximum doses of spartein sulphate followed intravenously in ten to twenty minutes by adrenalin solution, 0.2 c.c., and the rabbits were killed at varying intervals. At a four-hour interval there was both macroscopic and microscopic congestion of the left ventricle; at twenty-four and thirty-two-hour intervals there was bloody fluid in the body cavities, areas of congestion over the surfaces of the heart and microscopically a diffuse increased cellularity with capillary congestion and muscle degeneration. At five-day intervals the same picture was seen only more advanced and more extensive with greater muscle degeneration. Grossly there was a roughened area on the surface of the left ventricle. Those rabbits surviving two injections showed very great increased cellularity and marked muscle degeneration.

The histology of the myocardial lesions so produced can be described somewhat more consecutively as follows: Very shortly after a dose of spartein sulphate is given, especially when this is followed by an intravenous injection of adrenalin chlorid, a capillary congestion appears (Fig. 1), whether the drugs have been given several times previously or not. The congestion is probably transitory, for a later stage is represented by interstitial edema (Fig. 2), with which may be associated some connective tissue proliferation (Figs. 2 and 3). Another effect of these drugs is the production of cellular foci made up of lymphoid, plasma and young connective tissue cells (Fig. 4), usually about necrosed or severely injured muscle cells (Fig. 4). At other times the connective tissue proliferation is rather more diffuse, replacing muscle cells and extending among and separating degenerated muscle cells (Figs. 5 and 6). The exact histological picture varies with the age of the lesion. In some hearts a quite actively proliferating cellular stroma is seen (Figs. 5 and 6), in others there is adult connective tissue but slightly infiltrated with cells (Fig. 7).

From these results it appears that subcutaneous doses of spartein, followed intravenously by adrenalin, as well as small doses of spartein, followed by adrenalin, both intravenously, produce a moderate cellularity with slight muscle hypertrophy, while maximum doses of spartein, followed by adrenalin, both given intravenously, produce very marked cellularity, which goes on to fibrous tissue formation associated with extensive degeneration of the muscle. This latter method seems the most satisfactory procedure for producing chronic myocarditis. By comparing

these lesions with the descriptions of hypertrophy found in the human heart as described by Albrecht,[30] Krehl[31] and others,[32] there seems to be a striking familiarty.

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STUDY XI. EXPERIMENTAL PERICARDITIS PRODUCED BY SPARTEIN SULPHATE AND ADRENALIN CHLORID*

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This paper is a study of the pericardia of the hearts of rabbits used in the production of experimental myocarditis by the injection of spartein sulphate and adrenalin chlorid. The work was carried on in the laboratory of the Theory and Practice of Physic in the Medical School of Harvard University.

There seems to have been very little previous work done on experimental pericarditis. Fleisher and Loeb[33] in their paper on Experimental Myocarditis mention an accompanying pericarditis, but they do not describe it. In a second paper[34] they state that six rabbits in a series of forty-two animals showed a pericarditis in five associated with pneumonia. They state that "it appears improbable that . . . the injection of spartein and adrenalin produced the pericarditic lesion in the same direct way as it did the myocarditis." No other references to lesions of this type were found.

Rabbits were the only animals used in the experiments here described. For convenience these animals are grouped into five series in which the spartein sulphate and adrenalin chlorid were used by different methods in order to determine the most satisfactory procedure for producing experimental cardiac lesions. For a description of each series with details of methods used and results obtained, the reader is referred to the previous paper, "Experimental Myocarditis Produced by Spartein Sulphate and Adrenalin Chlorid." In this place only the pericardial changes will be described.

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30. Albrecht: Der Herzmuskel, Berlin, 1903.

31. Krehl: Deutsch. Arch. f. klin. Med., 1890, xlvi, 454; 1891, xlviii, 414; Nothnagel's Specielle Pathologie und Therapie, xv.

32. Stadler: Deutsch. Arch. f. klin. Med., 1907, xci, 98.

33. Fleisher and Loeb: Experimental Myocarditis, THE ARCH. INT. MED., 1909, iii, 78.

34. Fleisher and Loeb: Further Investigations in Experimental Myocarditis, THE ARCHIVES INT. MED., 1910, vi, 427.

SERIES 1.—Four rabbits injected intravenously with spartein sulphate[35] 0.025 gm. without adrenalin chlorid. One rabbit killed a few minutes after injection showed no lesion of the pericardium. Another was killed four hours after injection and showed an area of congestion in the surface of the left ventricle, and microscopically an occasional red blood-cell in the fibrous tissue of the pericardium. A third was injected every three days for twenty-five injections and another rabbit for thirty injections. Both of these showed in their pericardia a few scattered red blood-cells and an occasional area where there were many red cells. In these two rabbits the spartein was gradually increased until they received 0.05 gm. several times.

SERIES 2.—Twenty-four rabbits were selected, weighing between 1100 and 1400 gm., paired according to weights and were injected subcutaneously at three-day intervals with spartein sulphate 0.025 gm., followed subcutaneously in three to five minutes with adrenalin chlorid 0.2 c.c. of a 1 to 1000 solution.[36] Two rabbits were killed three days following the first injection, two more three days following the second injection, and this was repeated until the last two rabbits of this series were killed. Of these twenty-four rabbits, two were discarded after three injections because one of the rabbits contracted an infection. No macroscopic or microscopic lesions could be observed in the pericardium of any of the rabbits of this series.

Two more rabbits were injected subcutaneously with the same dosage as in the preceding series every day for six weeks and then every other day for six additional weeks. These two rabbits showed no macroscopic or microscopic lesions of the pericardium.

SERIES 3.—Eight rabbits were injected subcutaneously with spartein sulphate 0.025 gm., followed in about ten minutes intravenously by adrenalin chlorid 0.2 c.c., 1 to 1000 solution.

Rabbit 274 was injected subcutaneously with spartein sulphate 0.025 gm., followed intravenously in ten minutes by adrenalin chlorid 0.2 c.c., 1 to 1000 solution. This animal died twenty minutes later with respiratory paralysis and convulsions. Microscopically the pericardium was congested and edematous, red blood-cells were scattered throughout the fibrous tissue. Rabbit 273 similarly injected, died the same day and showed a slight hemorrhagic exudation into the pericardium (Fig. 19).

Rabbit 279, weight 1450 gm., was injected subcutaneously with spartein sulphate 0.025 gm., followed in ten minutes by adrenalin chlorid 0.2 c.c., 1 to 1000 solution. Five days later the same was repeated and the rabbit died about ten minutes following this injection. At autopsy there was an increased amount of a straw-colored fluid in all the body cavities. Microscopically there was slight thickening of the pericardium with increased cellularity, and edema, especially of that part of the pericardium adjoining the myocardium (Fig. 20). The cells present were of the young connective tissue and lymphoid types, with a rare polynuclear leukocyte. The pericardium of the left ventricle was the seat of this lesion.

Rabbit 268, weight 1580 gm., was injected subcutaneously with spartein sulphate 0.025 gm., followed intravenously in ten minutes by adrenalin chlorid 0.2 c.c., 1 to 1,000 solution. Three days later the injection was repeated, and again in four days, when the rabbit died five minutes after the spartein injection. Thus this animal survived two injections extending over a period of seven days. At autopsy there was a small amount of clear straw-colored fluid in all the body cavities. Microscopically there was slight thickening of the pericardium with slight edema and congestion, increased vascularity and cellularity (Fig. 21).

Rabbit 277, weight 1480 gm., was injected subcutaneously with spartein sulphate 0.025 gm., followed intravenously in ten minutes by adrenalin chlorid

35. Merck's preparation of spartein sulphate was used throughout.

36. Parke, Davis & Co.'s preparation of adrenalin chlorid solution was used throughout.

0.2 c.c., 1 to 1000 solution, this being repeated every three days for a period of twelve days, thus four injections were given. The rabbit died a few minutes after the last injection, only surviving three injections. At autopsy considerable free bloody fluid was present in all the cavities and in addition considerable fibrin in the pericardial cavity, with slight roughening of the surface of the left ventricle. The heart was large. Microscopically the same general picture was seen as in No. 268, but the process was more extensive, the whole thickness of the pericardium being involved, and the pericardium was also more cellular.

Two other rabbits were injected over a long period of time. Rabbit 278, weight 1480 gm., received thirteen injections at three-day intervals, and No. 285, weight 2200 gm., was given thirty injections during a period of three months, both of these rabbits getting the same doses under the same conditions as the previously described animals. Microscopically there was a slight increased cellularity of the connective tissue type. The cells appeared in foci scattered along the juncture of the pericardium and myocardium.

SERIES 4.—Here six rabbits were used and were injected intravenously with small doses of spartein and adrenalin.

Rabbit 267, weight 1520 gm., was injected intravenously with spartein sulphate 0.025 gm., followed intravenously in ten to twenty minutes by adrenalin chlorid 0.2 c.c., 1 to 1000 solution. This was repeated seven times at three-day intervals for a period of about a month, when the rabbit died immediately following the ninth injection. Microscopically in places in the pericardium of the left ventricle there were foci of lymphoid cells and young connective tissue cells with congestion. In other places there were chiefly young connective tissue cells, and in still other places only red blood-cells were noted.

Rabbit 272, weight 2750 gm., was injected intravenously with varying doses of spartein sulphate from 0.025 gm. to 0.05 gm., followed intravenously in ten to twenty minutes by adrenalin chlorid 0.2 c.c., 1 to 1000 solution. These injections extended over a period of three months at three-day intervals, so that the rabbit received in all twenty-five injections. At autopsy the heart was large, firm, with whitish areas of thickening on the wall of the left ventricle. Microscopically a very similar picture to No. 267 was seen.

Rabbit 275, weight 2450 gm., was injected in the same manner and the same number of times as No. 267. At autopsy there was much fluid in the abdominal cavity. Microscopically a similar picture to that in No. 267 was seen with the exception that the right ventricle showed the lesion.

Rabbit 265, weight 1200 gm., was injected intravenously with spartein sulphate in varying doses from 0.0125 gm. to 0.025 gm., followed intravenously in ten to twenty minutes by adrenalin chlorid 0.2 c.c., 1 to 1000 solution, in all eighteen injections during two months' time at three-day intervals. Microscopically at the base of the left ventricle the denser pericardial layer was separated from the underlying muscle by a tissue of increased cellularity, with young connective tissue cells, plasma cells and red blood-cells.

Rabbit 282, weight 1920 gm., was injected intravenously with spartein sulphate 0.007 gm., followed intravenously in ten minutes by adrenalin chlorid 0.1 c.c., 1 to 1000 solution repeated at three-day intervals for seven times; then the spartein was increased to 0.008 gm. and the injections repeated at three-day intervals for seven more times, in all fourteen injections extending over two months' time. At autopsy there was fluid in the abdominal and thoracic cavities, and a muddy bloody fluid filled the pericardial cavity. The heart was very large, the left auricle and ventricle were very firm and thickened, with a white fibrous patch at the base of the left ventricle. Microscopically throughout the pericardium of both the left auricle and left ventricle there was considerable increased cellularity of the lymphocyte and young connective tissue types with edema and congestion. This was most marked at the myocardial margin.

SERIES 5.—In this series eleven rabbits were injected intravenously with spartein sulphate and adrenalin chlorid in the following way. Spartein sulphate was injected intravenously in maximum doses, that is, as large a dose as the

rabbit appeared able to stand. Shortly after such a dose the rabbit would seem very tired with rapid respiration and a rapid unsteady heart. After an interval of ten to twenty minutes adrenalin chlorid was injected intravenously with a dose of 0.2 c.c. of a 1 to 1000 solution. The adrenalin appeared to produce no marked effect except possibly to accentuate somewhat the already existing symptoms.

One of these rabbits, No. 276, was killed three minutes after the adrenalin injection, and nothing abnormal was seen.

Rabbit 290, weight 1480 gm., was injected intravenously with spartein sulphate 0.04 gm., followed intravenously in ten minutes by adrenalin chlorid 0.2 c.c. of a 1 to 1000 solution. This rabbit became very tired and listless, respiration rapid, heart rapid and fluttering, three hours later the heart seemed steadier, but the animal was very stupid. Four hours after injection the rabbit was killed. At autopsy the large blood-vessels were tied and the heart and pericardium were removed *in toto* without being opened in order to avoid hemorrhage within the pericardial cavity from trauma or mechanical causes; the heart and pericardium were hardened *in toto*. Macroscopically there was a bloody red area of congestion on the wall of the left ventricle near the center about 0.5 cm. in diameter. Microscopically there were areas of hemorrhage and edema in the pericardium of the left ventricle, also the pericardium was torn and raised away from the myocardium in numerous places where the congestion of the subpericardial myocardium was greatest.

The third rabbit, No. 296, weight 1750 gm., was injected intravenously with spartein sulphate 0.035 gm., followed intravenously in ten minutes by adrenalin chlorid 0.2 c.c. of a 1-to-1000 solution. The rabbit seemed very tired after this. It was killed twenty-four hours after injection. At autopsy the thoracic cavity contained much very bloody fluid and the pericardial cavity was filled with bloody fluid. The heart showed areas of congestion of a bright red color on the surface of the right auricle, to a slight extent on the left auricle, and on the surface of the left ventricle an area of dark brownish red color with slight peripheral congestion. The heart and the pericardium were removed intact after the large blood-vessels were tied, and thus were hardened. Microscopically the pericardium was somewhat thickened with slight increased cellularity, edema and congestion. The types of cells were lymphoid cells, an occasional leukocyte, young connective tissue and endothelial cells having faintly staining, hazy and indistinct nuclei placed centrally in a scanty, faintly staining protoplasm. The pericardium of both auricles and both ventricles was similarly affected, although more cellular in some areas than others. The outer pericardium or sac showed a similar picture.

A fourth rabbit, No. 293, received intravenously 0.04 gm. of spartein sulphate and ten minutes later intravenously 0.2 c.c. adrenalin chlorid, 1 to 1000 solution. This animal seemed very tired and quiet after the injection similarly to No. 296, and was killed at the end of thirty-two hours. At autopsy there was a slight amount of a straw-colored fluid in the abdominal cavity, very much and rather bloody fluid in the thoracic cavity, while the pericardial cavity was filled with a very bloody fluid, and the parietal pericardium seemed to be glued in places to the left ventricle. Areas of fresh hemorrhage were present on the right auricle, much more marked and wide-spread on the left ventricle. The heart and pericardium were removed and hardened intact as previously. Microscopically a very similar picture was found to that seen in No. 296, only slightly more advanced, more extensive and more cellular. In addition there were many more leukocytes and much fibrin. These sections were stained for bacteria but none could be made out. The pericardium of the left ventricle was most affected. The parietal pericardium showed a similar picture.

The fifth rabbit, No. 280, weight 1580 gm., was injected with spartein sulphate 0.03 gm., followed in about ten minutes by adrenalin chlorid 0.2 c.c., 1 to 1000 solution, both drugs given intravenously. After five days the rabbit was killed. At autopsy much free blood-stained fluid was found in the abdominal

cavity, with little flakes of fibrin floating on the intestines, still more bloody fluid in the thoracic cavity, and the pericardial cavity was filled with very bloody fluid. A small roughened area was present on the surface of the left ventricle. Microscopically the pericardium was slightly thickened. The normal fibrous tissue of the pericardium showed slight congestion, edema and a few young connective tissue cells. The area where the pericardium joins the myocardium was thickened with a greatly increased number of connective tissue cells, scattered lymphoid cells, increased vascularity with congestion, edema, and an occasional leukocyte. The left ventricle was affected.

The sixth rabbit of this series, No. 270, weight 2370 gm., was injected intravenously with spartein sulphate 0.025 gm., followed intravenously in fifteen minutes with adrenalin 0.2 c.c. The same was repeated three days later and the rabbit died four days after the second injection, that is seven days after the first injection. At autopsy the abdominal cavity contained 60 c.c. of free blood stained fluid, the thoracic cavity 18 c.c., and the pericardial cavity was filled with very bloody fluid. The heart muscle was pale. The heart and pericardium were removed *in toto*. Microscopically (Fig. 22) a similar picture was seen to that in No. 280, and in addition an acute process, so that the pericardium was considerably thickened.

The seventh rabbit, No. 292, weight 1750 gm., was injected intravenously with 0.03 gm. spartein sulphate followed intravenously in fifteen minutes by adrenalin chlorid 0.2 c.c., 1-to-1000 solution; this was repeated two days later and the animal was killed twenty-four hours after the second injection, that is, three days after the first injection. Macroscopically there was an area near the apex on the left ventricle of a brownish color, where the muscle was soft, pale and flabby. Microscopically a very similar picture to No. 296 and No. 270 was found, only with more thickening and more cells, more extensively distributed.

The description of a rabbit of another series of experiments is inserted here as it furnishes an intermediate stage in the pericardial lesion undoubtedly produced in the same way as in the preceding animal, though not the same procedure was followed. This is Rabbit 79, treated as follows: Spartein sulphate 0.021 gm. was given subcutaneously followed by adrenalin chlorid, 1 to 1,000 solution, 0.2 c.c., subcutaneously. These injections were repeated four times in the next four months in the same way, except that the last dose of adrenalin chlorid was given intravenously. At autopsy two weeks after the last injection, the pericardium appeared more opaque and thicker than normal. Microscopically in place of the rather thin, cell-poor pericardium there was a thick layer of vascular cellular connective tissue (Fig. 23) in every way similar to young granulation tissue.

Rabbit 266, weight 1240 gm., was injected intravenously with spartein sulphate 0.025 gm., followed intravenously in ten to twenty minutes by adrenalin chlorid 0.2 c.c. This was repeated at three-day intervals for five times. After injection the rabbit became so tired with rapid respiration that three days later the dose of spartein was reduced to 0.018 gm. followed in ten to twenty minutes by adrenalin 0.2 c.c., both intravenously. Again the rabbit was much exhausted and three days later the dose of spartein was reduced to 0.0125 gm., followed in ten to twenty minutes by adrenalin 0.2 c.c., both intravenously. The rabbit was much exhausted, tired and listless, with rapid respiration, but forceful and steady heart. The rabbit died three quarters of an hour later. At autopsy there was a slightly increased amount of muddy fluid in the pericardial cavity. Dense fibrous adhesions extended from the parietal pericardium to the auricle and ventricle of the left heart. Microscopically there was a much thickened cellular vascular pericardium with papilla formation on the surface of the left ventricle (Fig. 24), a typical granulation tissue.

The remaining rabbits of this series were duplicates of the above and will not be described.

Summary

Although the number of rabbits used in some of these experiments is rather small, fairly definite conclusions are evident.

Spartein sulphate in large doses, injected intravenously alone, will produce no lesion of the pericardium, except congestion. Five rabbits were used.

Spartein sulphate injected subcutaneously, followed by adrenalin chlorid subcutaneously, produces no lesion of the pericardium. In this series twenty-four rabbits were used.

Spartein sulphate injected subcutaneously, followed in ten minutes intravenously by adrenalin chlorid, 0.2 c.c of a 1-to-1,000 solution, does produce a pericarditis. First, congestion and edema are produced, these being noted as early as twenty-five minutes after the adrenalin injection. Later there is hemorrhage into the pericardial cavity. At a five-day interval there is an increased cellularity, the cells being of the young connective tissue and lymphoid types. The same drugs repeated more frequently in the same dosage and the same manner produce a more advanced and more extensive lesion with increased vascularity. At autopsy in those animals surviving for a few days, fluid is found in the body cavities. In all rabbits the lesion is in the pericardium of the left ventricle. Eight rabbits were used in this series.

In the series of six rabbits injected intravenously with small doses of spartein sulphate, followed in ten to twenty minutes intravenously by adrenalin chlorid, 0.2 c.c. of a 1-to-1,000 solution, an increased cellularity is produced. The lesion is usually confined to the pericardium of the left ventricle (with the exception of one rabbit, in which both the right and left ventricles were affected, and one rabbit in which only the pericardium of the right ventricle was affected).

The series of eleven rabbits injected intravenously with spartein sulphate in maximum doses, followed intravenously by adrenalin chlorid, 0.2 c.c., show a progressive lesion of the pericardium depending upon the length of time the animal survived and the number of doses given. At a four-hour interval a macroscopic area of congestion over the surface of the left ventricle, and microscopically hemorrhage and edema of the pericardium of the left ventricle were seen. At twenty-four and thirty-two hour intervals macroscopically were noted bloody fluid in the pericardial cavity, and areas of old congestion, and microscopically increased cellularity of the young connective tissue and lymphoid types with a few leukocytes; at a five-day interval bloody fluid and roughening of the left ventricle, microscopically increased cellularity and vascularity with edema and congestion. Those rabbits surviving two injections and extending over periods of three and seven days showed macroscopically a similar lesion of the pericardium of the left ventricle with bloody fluid, and

microscopically a chronic plus and acute lesion. The last rabbit surviving six very large injections given in the same manner as those described previously in this series, showed at autopsy a muddy fluid with fibrous adhesions between parietal pericardium and left side of heart. Microscopically there was a much thickened cellular vascular pericardium with papilla formation over the left ventricle. It is evident that maximum doses of spartein followed by adrenalin, both given intravenously, produce the most marked pericardial lesion.

The mechanism of the production of this pericardial lesion appears to be simple. As the result of the use of spartein sulphate and adrenalin chlorid in the ways described above certain lesions of the myocardium associated with congestion are produced. In a certain number of instances this congestion is very marked, and associated with it there is exudation into the pericardial cavity, probably both serous and hemorrhagic in nature. This exudation is in part undoubtedly absorbed, but in a considerable number of animals absorption does not take place quickly and organization follows. This condition associated with cellular infiltration and proliferation in the pericardial layer itself gradually leads to a thickening of the pericardium with the formation of typical granulation tissue and adhesions, with as a final result the picture of a chronic proliferative pericarditis.

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STUDY XII. EXPERIMENTAL ENDOCARDITIS PRODUCED BY SPARTEIN SULPHATE AND ADRENALIN CHLORID *

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In various published studies of experimental cardiac lesions most attention has been given to lesions of the myocardium and the valves. No description of certain changes sometimes found in the endocardium lining the ventricular cavities has come to my notice, and yet these changes are not infrequent in rabbits that have received spartein sulphate and adrenalin chlorid given in different combinations;[37] they were found in fourteen of a group of fifty-one rabbits so treated, even though in each rabbit only a relatively small portion of the entire heart was submitted to microscopic study. For these reasons it seems desirable to describe the endocardial lesions found in rabbits after the almost simultaneous injection of spartein sulphate and adrenalin chlorid. For such a study there were available in the Laboratory of the Theory and Practice of Physic

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37. For details of methods of dosage used in these experiments see series 2, 3, 4 and 5 in the paper by Walker on Experimental Myocarditis in this issue.

sections from hearts of rabbits that had been thus treated by Drs. Walker and Dana for the purpose of studying other cardiac changes.

The endocardial lesions to be described are more common in the left ventricle than in the right. Similar lesions, usually less developed, were noted sometimes in the auricles, but in only a few hearts were the auricles examined so that no statement as to the relative frequency of the lesion in auricles and ventricles can be given. Furthermore no exact statement as to relative frequency in the two ventricles is attempted for not all parts of either cavity were examined. Cross-sections were made through about half of the circumference of each ventricle and a portion of the interventricular septum a short distance below the auriculoventricular groove in all hearts and in some hearts sections in addition were made at right angles to the plane of the former. As far as can be judged from these the lesion is more commonly present or more fully developed in the left than in the right ventricle, thus corresponding to the distribution of myocardial lesions as described by Fleisher and Loeb,[38] and by Walker.[37] The lesion appears not to occur with any frequency if at all in the valves, at least the aortic and mitral valves were studied histologically and found normal in five of the fourteen rabbits that showed changes in the endocardium lining the cardiac cavities, and in five other rabbits with myocardial lesions.

The lesion found in these animals is entitled to be called endocarditis in that it is a progressive proliferative lesion, in sequence to injury to the endocardium associated with myocardial injury. It follows the use of certain drugs or chemicals given in combination. Whether they are caused mechanically as believed by Fleisher and Loeb for the myocardial lesions, whether they are a result of direct toxic action of the drugs, or whether they represent merely the extension to the endocardial surface of the myocardial lesion was not evident from the histological method of study here used.

The earliest change in the endocardium consists in a slight focal proliferation of the endothelium lining the cardiac cavity with an accompanying edema of the subendothelial connective tissue. Instead of the usual flattened type of endothelial cells you see more distinctly cuboidal cells with round or oval nuclei rather closely crowded together. The cells have increased in number and their nuclei are richer in chromatin.

This is well shown in Figure 25 from Rabbit 268, which received on December 17 spartein sulphate 0.025 gm. subcutaneously, followed by adrenalin chlorid, 0.2 c.c. of a 1-to-1000 solution intravenously and in which these doses were repeated on December 20 and December 24, the animal dying on the same day as the last injections. In Figure 25 the extreme left-hand portion of the endocardium shows normal endothelium, while passing from this end the cells show

38. Fleisher and Loeb: THE ARCHIVES INT. MED., 1909, iii, 78, and 1910, vi, 427.

increasingly well the changes described above. Where the endothelium shows most departure from the normal flat type the subendothelial connective tissue shows slight edema and very moderate cell infiltration (Figure 25).

Rabbit 272 received many more intravenous injections of smaller amounts of spartein sulphate and adrenalin chlorid, twenty-five in all, between December 17 and February 19, and showed a very similar lesion of the endocardium. Rabbit 296 was given spartein sulphate 0.035 gm. intravenously, followed by adrenalin chlorid 0.2 c.c. of a 1-to-1000 solution, and was killed the next day. This animal showed a slight focal proliferation of the endothelium. Rabbit 270 had two intravenous injections of spartein sulphate 0.025 gm. and adrenalin chlorid 0.2 c.c. of a 1-to-1000 solution three days apart and died four days after the last injection. It showed the endothelial proliferation already described and in addition in places there was considerable thickening of the endocardial layer so that instead of the normal endocardium there was a layer of young connective tissue quite cellular in character.

The endocardial thickening just described in Rabbit 270 represents a somewhat later stage of the endocarditic process in which the subendothelial connective tissue layer is thickened and cellular. The cellularity is made up of young connective tissue cells and infiltrating lymphocytes and plasma cells. Rabbit 279 with two doses five days apart of spartein 0.025 subcutaneously and adrenalin chlorid 1 to 1000 solution 0.2 c.c. intravenously showed several foci of cellular thickened endocardium as did Rabbit 79 after five doses between December 12 and April 24 (Figs. 26, 27 and 28). Rabbits 280 and 292, treated very similarly to Rabbit 279 showed quite the same appearance, while Rabbit 283, treated very similarly to Rabbit 272, i. e., with numerous smaller doses, showed about the same degree of focal thickening, but without the cellularity found in the others. Rabbit 172 with four doses, both drugs subcutaneously, from October 30 to December 8, was very like Rabbit 283. Rabbit 165 after seven subcutaneous injections of spartein and adrenalin between October 27 and November 17 showed an area of thickened cellular endocardium. Rabbit 277 with four injections, spartein subcutaneously and adrenalin intravenously, January 5 to 17, and Rabbit 267, with eight intravenous injections of spartein and adrenalin December 17 to January 24, showed the same general process more extensive than in Rabbit 279.

Rabbit 282 with fourteen intravenous injections of spartein 0.007 to 0.008 gm. and adrenalin 0.1 of a 1-to-1000 solution given at three-day intervals showed a more advanced process in which the endocardium was more extensively thickened, and this thickened endocardium was only moderately cellular. In Rabbit 266 the most extensive change was encountered. This animal was injected intravenously with spartein 0.020 to 0.025 gm., followed by adrenalin 0.2 c.c. at three-day intervals for five injections. The dose of spartein was then reduced to 0.18 gm. and 0.0125 gm., respectively, for two more doses at three-day intervals. The rabbit died shortly after the last, and the endocardium was found much thickened though not very cellular (Figs. 29 and 30). In some places in this rabbit thickened endocardium was directly continuous with areas of newly formed connective tissue replacing muscle cells of the myocardium (Fig. 31).

Summary

In rabbits after the injection of spartein sulphate followed by adrenalin chlorid there develops a proliferative lesion of the endocardium lining the cardiac cavity. This is probably a quite frequent lesion usually accompanying myocardial and pericardial lesions, as it was found in fourteen of a series of fifty-one hearts, even though relatively very small portions of the endocardium were examined in each heart. The earliest change observed consisted in a slight proliferation of the endothelium

and edema of the subendothelial connective tissue. A more advanced stage shows proliferative thickening of the endocardium reaching a considerable degree in the most advanced lesion obtained in this series.

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STUDY XIII. MYOCARDIAL LESIONS PRODUCED BY RENAL IRRITANTS (URANIUM, ARSENIC AND POTASSIUM BICHROMATE)*

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The lesions of the myocardium described in this paper are those lesions of the hearts taken from animals used in the experimental production of chronic nephritis. Dr. R. M. Smith, under the direction and supervision of Dr. H. A. Christian in the laboratory of the Department of the Theory and Practice of Physic, did this work on chronic nephritis. Mostly rabbits were used, but a few guinea-pigs were tried, although not very successfully for the kidney work, since they would not survive sufficiently large amounts of the drugs. An aqueous solution of uranium nitrate in doses varying from 0.0005 to 0.005 gm., an aqueous solution of potassium bichromate in varying amounts of a 1 per cent. and a 5 per cent. solution and arsenic in the form of Fowler's solution in 8 and 10 minim doses were used. All drugs were used by subcutaneous injection and, in addition, in a few instances, Fowler's solution was given by the stomach-tube. For a detailed description of the methods employed, the results obtained and the protocols, etc., I refer to Dr. Smith's paper on "Experimental Chronic Nephritis," this issue. The hearts of these animals are considered as controls to those used in the experimental production of myocarditis by spartein sulphate and adrenalin chlorid. In this paper only that portion of each protocol which deals with a pathological change in the circulatory system will be mentioned.

A series of thirteen rabbits of varying weights were injected subcutaneously with 0.001 and 0.002 gm. of uranium nitrate at varying intervals.

Rabbit 259, weight 1500 gm., was injected subcutaneously with 0.002 gm. of uranium nitrate every three or four days; in all, four injections were given in twenty-one days, and the rabbit died three days after the last injection. Nothing macroscopically abnormal was noted at autopsy. Microscopically, there were present in the myocardium foci of young connective tissue cells; these foci were quite extensive and very frequent, and the muscle was somewhat replaced by them.

Rabbit 260, weight 1575 gm., No. 261, weight 1760 gm., No. 264, weight 2070 gm. were all injected subcutaneously every three or four days with 0.002 gm. of uranium nitrate for fourteen times, extending over a period of two months. At autopsy macroscopically nothing pathological was found. Microscopically,

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the myocardium of each rabbit showed foci of young connective tissue cells with fibrils, lymphoid and plasma cells. These foci were fairly extensive and frequent. This picture was very similar to that in Rabbit 259 previously described, except that some foci seemed to be made up of younger connective tissue cells and thus more recent lesions, while other foci appeared older and more advanced. These foci more or less replaced the muscle.

Rabbits 207, 208, 221 and 227, weighing respectively 1530, 1740, 1435, 1460 and 1345 gm., were injected subcutaneously with 0.002 gm. of uranium nitrate every three or four days during a period of four months, thirty injections in all. Rabbits 207 and 208 were killed four weeks after the last injection, and at autopsy nothing grossly pathological was noted with the exception of an excess in the amount of fluid in the body cavities of Rabbit 208. The fluid of the pericardial cavity of Rabbit 208 appeared to be considerably increased, and the heart was large. Microscopically, the myocardium of Rabbit 207 was markedly congested with quite marked infiltration with lymphoid cells, especially the subpericardial myocardium. In addition there was a moderate increase of young connective tissue and lymphoid cells, diffusely, and in small foci throughout the myocardium. The myocardium of Rabbit 208 showed a moderate diffuse young connective tissue and lymphoid cell infiltration. In addition, at the base of the left ventricle there was a large area of young connective tissue cells with fibrils, large numbers of leukocytes and lymphocytes. In this area the muscle, which appeared to be hypertrophied, was more or less replaced by the above cells and the walls of the blood-vessels at this place were infiltrated with similar cells. Rabbit 209 was killed six weeks after the last injection. At autopsy there was much fluid in all the body cavities, and the heart was large. Microscopically there was an extremely slight increase of young connective tissue cells in small diffuse foci. Rabbit 221 was killed three days after the last injection. The organs appeared normal at autopsy. Microscopically there was marked congestion and some edema of the myocardium with a slight amount of young connective tissue, lymphoid and leukocyte cell infiltration, diffusely situated, but most marked in the subpericardial myocardium. Rabbit 227 died during an edema experiment, six weeks after the last injection. At autopsy the only thing pathological noted was a large amount of a free, very bloody fluid in the abdominal cavity. Microscopically there was an extremely slight increase of young connective tissue cells in small diffuse foci.

Rabbit 226, weight 1310 gm., was injected subcutaneously with 0.002 gm. of uranium nitrate every three or four days for seven injections. The rabbit died two days after the last injection. At autopsy nothing abnormal was noted except that the aorta was very brittle, parchment-like and crumbled on pressure. Microscopically a similar picture to that in Rabbit 227 was seen.

Rabbits 124, 129 and 130, weighing respectively 2,000, 1,520 and 2,000 gm., were each injected subcutaneously with 0.001 gm. of uranium nitrate daily for eight days, after which the amount of uranium nitrate was increased to 0.002 gm., and injected subcutaneously daily for nine more times. After this 0.002 gm. of uranium nitrate was injected subcutaneously every three or four days for twenty-five injections. Altogether these three rabbits received forty-two injections in five and a half months. Rabbit 130 was killed three days after the last injection, Rabbit 129 ten days, and Rabbit 124 was killed four weeks after the last injection. At autopsy nothing pathological was seen in any animal. Microscopically Rabbit 130 showed slight congestion and very slight young connective tissue and lymphoid cell increase, diffusely situated in the myocardium. The myocardium of Rabbit 129 was congested in places, and one small focus of young connective tissue and lymphoid cells was noted in the wall of the left ventricle. Rabbit 124, microscopically showed very slight young connective tissue and lymphoid cell infiltration throughout the myocardium with slight congestion, which was more marked in the subpericardial myocardium. In addition, the walls of the blood-vessels appeared to be infiltrated with young connective tissue cells.

Therefore, to summarize the findings in this series of thirteen rabbits, three rabbits which were injected daily for seventeen days and every three or four days for twenty-five times, showed only a very slight increased cellularity of the myocardium. Four other rabbits injected a less number of times showed a similar picture. The remaining six rabbits showed a fairly marked lesion of the myocardium, chiefly foci of young connective tissue and lymphoid cells, which replaced to a more or less extent the muscle of the myocardium. However, in none of these rabbits was the lesion very marked, or very destructive, and in none was it extensive.

A second series of twenty-two rabbits of varying weights was injected subcutaneously with 0.005 gm. of uranium nitrate at three-week intervals, this interval having been found to give the most satisfactory lesions in the kidneys.

Rabbits 198, 199 and 200, weights respectively 1190, 1140 and 1190 gm., were injected subcutaneously with 0.005 gm. of uranium nitrate and all died five days after being injected. At autopsy all three rabbits had a large amount of free bloody fluid in the abdominal, thoracic and pericardial cavities. Microscopically there was congestion of the subpericardial myocardium with edema, most marked in Rabbit 199 and less marked in Rabbit 200. In addition, there was a slight diffuse infiltration of the myocardium with young connective tissue and lymphoid cells and leukocytes. In Rabbit 198 the cellular increase was more marked than in Rabbits 199 and 200.

Rabbits 246, weight 1520 gm., and 251, weight 1690 gm., were injected the same as the ones just described, and these died seven days after being injected. At autopsy both rabbits had an excess amount of fluid, straw-colored, in the abdominal cavity. Microscopically both rabbits showed a slight diffuse young connective tissue and lymphoid cell infiltration of the myocardium.

Rabbit 128, weight 1330 gm., was injected subcutaneously with 0.005 gm. of uranium nitrate, and at the end of three weeks this was repeated. The rabbit died twelve days after the second injection. At autopsy nothing pathological was noted. Microscopically there was congestion of the myocardium with very slight increase of young connective tissue and lymphoid cells, and very slight thickening of the walls of the blood vessel. In addition, the myocardium of the left ventricle at the base of the heart contained a large area of cells of the young connective tissue and lymphoid cell types. In this area the muscle was almost replaced by the cellularity, only shreds of muscle were evident.

Rabbit 190, weight 1390 gm., was injected the same as No. 128, except that it got one more injection, and died eleven days after the last, or third injection. At autopsy the aorta was stiff and like parchment, and the heart muscle appeared mottled with whitish specks. Microscopically there was a very marked patchy infiltration of the myocardium with young connective tissue cells, and fine connective tissue fibrils. These areas of cellularity were quite extensive and frequent and replaced the muscle to a more or less extent. There was an increase of young connective tissue about the walls of the blood-vessels, which were slightly thickened.

Rabbits 247, 248, 249, 250 and 252, weighing respectively 1430, 1720, 2080, 2380 and 2480 gm., were all injected subcutaneously with 0.005 gm. of uranium nitrate five times, with three-week intervals between the injections, extending over a period of three months. These rabbits were killed respectively six weeks, four weeks, three days, seven weeks, and six weeks after the last injection. At autopsy nothing pathological was noted in any of the rabbits, except in Rabbit 252, which had a large, pale and flabby heart, and there was a slight excess of fluid stained with blood in the abdominal, thoracic and pericardial cavities.

Microscopically Rabbit 247 showed foci of young connective tissue cells with fibrils replacing the muscles to a slight extent. In Rabbits 248 and 250 the myocardium was very slightly infiltrated with young connective tissue and lymphoid cells diffusely situated. Microscopically the myocardium of Rabbits 249 and 252 showed a slight diffuse increase of young connective tissue and lymphoid cells. In addition there was an area in the myocardium of the left ventricle where young connective tissue cells with fibers invade the already hypertrophied muscle. The muscle looked like a network on which the new young tissue was growing.

Rabbits 189, 191, 192, 193, 194, 195, 196 and 197, weighing respectively 1390, 1490, 1470, 2500, 1280, 1170, 1215, and 1145 gm., were all injected subcutaneously with 0.005 gm. of uranium nitrate seven times at three-week intervals during a period of four months. These rabbits were killed at varying intervals, four weeks, two weeks, two days, four weeks, six weeks, four weeks, six weeks, and seven weeks respectively after the last injection. At autopsy the heart muscle of Rabbit 189 was of a grayish color and cut with resistance. The other rabbits showed no pathological change of the circulatory system. Microscopically the myocardium of Rabbit 189 was rather markedly infiltrated with young connective tissue and lymphoid cells, also there were areas where the hypertrophied muscle was replaced by older fibrous tissue through which young connective tissue and lymphoid cells were scattered. The subpericardial myocardium was congested and there was a diffuse cellularity of the two above-mentioned types. The walls of the blood-vessels seemed to be thickened and infiltrated with young connective tissue cells. The myocardium of Rabbits 191, 192 and 193 was very slightly infiltrated diffusely with young connective tissue cells and the muscle was somewhat hypertrophied. The last rabbit, No. 193, had a more marked cellular increase than the two former. Rabbit 194 showed a very slight diffuse young connective tissue and lymphoid cell increase. The myocardium of Rabbit 195 was congested, edematous, quite markedly infiltrated with lymphoid cells, a few leukocytes and young connective tissue cells. Rabbits 196 and 197 showed a similar picture. There was a very slight diffuse increased cellularity with occasional foci of young connective tissue and lymphoid cells, also mild congestion and slight muscle hypertrophy.

Rabbit 178, weight 1580 gm., was injected subcutaneously like the above rabbits for six times and killed nine weeks after the last injection. Microscopically there was slight diffuse young connective tissue and lymphoid cell increase with slight hypertrophy of the muscle of the myocardium.

Rabbits 177 and 187, weighing respectively 1250 and 1360 gm., were injected subcutaneously with 0.004 gm. of uranium nitrate six times at three-week intervals and were killed four and nine weeks after the last injection. The myocardium of Rabbit 177 showed a very slight diffuse young connective tissue and lymphoid cell increase. The walls of the blood-vessels were thickened and the intimal cells appeared to be proliferated. The myocardium of Rabbit 187 showed a more marked lesion. The young connective tissue cells had fibrils, and these had invaded degenerated muscle fibers, and the new tissue more or less replaced the muscle. A few lymphoid cells were noted.

In this series of twenty-two rabbits, the myocardium of ten rabbits showed only a very slight increased cellularity. The myocardium of the remaining twelve rabbits showed a fairly marked increased cellularity of the young connective tissue and lymphoid cell types, situated diffusely and in foci, which caused degeneration of the muscle and more or less replaced it.

A third series consisted of guinea-pigs of varying weights injected subcutaneously with varying amounts of uranium nitrate, ranging from

0.0005 gm. to 0.003 gm., at varying intervals. Nothing grossly pathological was found in these animals.

Guinea-Pig 175, weight 475 gm., was injected subcutaneously with 0.001 gm. of uranium nitrate and died four weeks later. Microscopically there was quite a marked diffuse increased cellularity of the young connective tissue and lymphoid cell types, with slight congestion of the myocardium. Also these cells were present in small foci.

Guinea-Pig 140, weight 440 gm., was injected subcutaneously with 0.001 gm. of uranium nitrate and this was repeated every three weeks for eight injections. The guinea-pig died ten days after the last injection. Microscopically the myocardium showed a similar picture to Guinea-Pig 175.

Guinea-Pigs 139 and 142, weights 685 and 560 gm., were injected subcutaneously with 0.0005 gm. of uranium nitrate every other day for ten injections. Then the amount of uranium was increased to 0.001 gm. and Guinea-Pig 142 died three weeks after this injection. Guinea-Pig 139 survived eight injections of 0.001 gm. each at three-week periods, and was killed ten days after the eighth injection. Microscopically the myocardium of each guinea-pig showed a similar picture, namely, a slight congestion and a diffuse slight young connective tissue increase with occasional foci of young connective tissue and lymphoid cells. The walls of the blood-vessels appeared to be slightly thickened.

Guinea-Pigs 186 and 241, weights 390 and 485 gm., were injected subcutaneously with 0.001 gm. of uranium nitrate and this was similarly repeated four times with three-week intervals between each injection. Guinea-Pig 186 died ten days after the last injection, and Guinea-Pig 241 died four days after the last injection. Microscopically the myocardium of Guinea-Pig 186 was slightly congested and was infiltrated with foci of young connective tissue and lymphoid cells. The walls of the blood-vessels appeared considerably thickened and infiltrated with young connective tissue cells. The myocardium of Guinea-Pig 241 was diffusely infiltrated with young connective tissue and lymphoid cells. This was most marked in the subpericardial myocardium. The walls of the blood-vessels were thickened with an increase of young connective tissue cells.

Guinea-Pig 176, weight 550 gm., was injected subcutaneously with 0.001 gm. of uranium nitrate six times at three-week intervals, and was killed ten days after the last injection. Microscopically the myocardium was considerably congested and moderately infiltrated with lymphoid and young connective tissue cells and a few leukocytes.

Guinea-Pig 185, weight 670 gm., was injected subcutaneously with 0.002 gm. six times at three-week intervals and was killed ten days after the last injection. Microscopically there was a slight diffuse young connective tissue and lymphoid cellularity, although the same types of cells appeared in small scattered foci. The above cellularity was most marked in the subpericardial myocardium. There was considerable congestion. The walls of the blood-vessels were slightly thickened.

Guinea-Pig 229, weight 400 gm., was injected subcutaneously with 0.001 gm. of uranium nitrate five times at three-week intervals and the guinea-pig was killed five weeks after the last injection. Microscopically the myocardium was markedly congested and considerably infiltrated diffusely with young connective tissue cells. The muscle appeared to be hypertrophied. The vessel walls were somewhat thickened.

Guinea-Pig 188, weight 450 gm., was injected subcutaneously with 0.003 gm. of uranium nitrate, and the guinea-pig died six days later. The myocardium, microscopically, showed congestion and a slight diffuse young connective tissue cellularity.

This series of ten guinea-pigs received a similar amount of uranium nitrate in proportion by weight as did the rabbits in the previous series.

and they likewise showed a similar lesion of the myocardium, which was possibly more marked, and more extensive in proportion to their weights than the previous series of rabbits showed. The thickening of the walls of the blood-vessels was more striking and more constant in this series.

Another series of rabbits were experimented on with Fowler's solution, which was injected subcutaneously in 8 and 10 minim doses, and also was given in similar amounts, with equal parts of water, by stomach tube. Fourteen rabbits were used in this series.

Rabbit 121, weight 2250 gm., was injected subcutaneously daily with 4 minims of Fowler's solution twice, 7 minims once, and after this with 10 minims daily for nine times. The injections were then suspended for one month, on account of severe sloughing of the abdominal wall at the site of the previous injections, and also because the urine examination showed that the rabbit had a marked lesion of the kidneys. At the end of a month 10 minims of Fowler's solution with equal parts of water were given by the stomach tube and this was repeated twice every other day. The rabbit died three days after the last dose. Altogether the rabbit received twelve subcutaneous injections daily and three doses by the stomach-tube. At autopsy the heart was very large. Microscopically the myocardium was congested and there was one area of hemorrhage at the base of the left ventricle near the septum. The subpericardial myocardium appeared to be recently congested.

Rabbit 138, weight 2730 gm., was injected subcutaneously with 10 minims of Fowler's solution, and this was repeated two days later. Three weeks later 10 minims of Fowler's solution was given by the stomach-tube. This was repeated three days later, and again five days later. The rabbit died two days after the third dose by the stomach tube. At autopsy the heart seemed large. Microscopically in the myocardium there were areas of fibrous tissue replacing the muscle, which was left as little fragments scattered through the fibrous tissue. In other areas there was infiltration with young connective tissue and lymphoid cells. The papillary muscles were very fibrous.

Rabbit 235, weight 2520 gm., was given 10 minims of Fowler's solution by the stomach-tube. This was repeated six times at weekly periods and three times at ten-day intervals. The rabbit was killed nine weeks later. The heart was large. Microscopically there were foci of young connective tissue cells replacing the muscle of the myocardium.

Rabbits 236 and 238, weighing 1920 and 1730 gm., were each given 8 minims of Fowler's solution by stomach tube and this was repeated every seven days for six times, and after this every ten days for three more times. The rabbits were killed six and eight weeks respectively after the last dose. At autopsy nothing grossly pathological was found. Microscopically Rabbit 236 showed an extremely slight diffuse and an occasional small focus of young connective tissue and lymphoid cellularity. Rabbit 238, microscopically, showed a slight diffuse young connective tissue cell infiltration of the myocardium, with muscle hypertrophy, and also very small foci of lymphoid cells. The walls of the blood-vessels were thickened and there was capillary congestion.

Rabbit 132, weight 2050 gm., was injected subcutaneously with 10 minims of Fowler's solution seven times in ten days and the rabbit died on the eleventh day. Nothing pathological was noted at autopsy. Microscopically there was a very slight young connective tissue cell increase diffusely with slight muscle hypertrophy and congestion of the myocardium, also there was a slight amount of old fibrous tissue infiltrated with young connective tissue cells, and a few small foci of these cells were scattered through the myocardium. The walls of the blood-vessels were thickened.

Rabbit 233, weight 1600 gm., was injected subcutaneously with 8 minims of Fowler's solution, and repeated seven times at weekly intervals and three

times more at ten-day periods, extending over a period of three months altogether. Six weeks after the last injection the rabbit was killed. At autopsy nothing pathological was noted. Microscopically there was congestion and a slight diffuse cellularity of the young connective tissue and lymphoid cell types, also these same cells were in foci. In addition, there were areas of young connective tissue cells with fibrils replacing the already hypertrophied muscle. The walls of the blood-vessels were thickened and infiltrated with young connective tissue cells.

Rabbits 239 and 243, weights 2250 and 2280 gm., were injected subcutaneously with 10 minims of Fowler's solution. In Rabbit 239 this was repeated every seven days for three times and the rabbit died seven days after the last injection. In Rabbit 243 this was repeated twice at weekly intervals and the rabbit died two days after the last injection. At autopsy Rabbit 239 showed no pathological lesion, but Rabbit 243 had an excess of fluid in the pericardium and the heart was very large. Microscopically both rabbits showed a similar lesion of the myocardium. There was a slightly increased cellularity, both diffusely and in small foci of the young connective tissue and lymphoid cell types, with moderate congestion and muscle hypertrophy. The walls of the blood-vessels were thickened.

Rabbits 253, 254, and 255, weighing 2250, 1950, and 2180 gm. respectively, were each injected subcutaneously with 10 minims of Fowler's solution, and this was repeated six times at ten-day intervals. The rabbits were killed eight and six weeks after the last injection. At autopsy nothing pathological was found. Microscopically Rabbits 253 and 254 showed a very slight young connective tissue cell increase of the myocardium. Rabbit 255 showed only marked congestion of the myocardium.

Rabbits 234 and 237, weighing 2470 and 1950 gm., were injected subcutaneously with 10 minims of Fowler's solution, repeated six times at weekly intervals and three times more at ten-day intervals. One rabbit was killed eight and the other six weeks after the last injection. At autopsy nothing pathological was noted. Microscopically Rabbit 234 had a slight diffuse young connective tissue and lymphoid cellularity of the myocardium with muscle hypertrophy. The walls of the blood-vessels were slightly thickened. The myocardium of Rabbit 237 showed young connective tissue and lymphoid cells diffusely and in foci with slight hypertrophy of the muscle.

In this series of fourteen rabbits all showed a more or less increased cellularity of the myocardium diffusely or in foci or both. In two rabbits there was only congestion of the myocardium, in six others a slight cellularity of the myocardium with slight hypertrophy of the muscle. In the remaining six rabbits the cellularity was more marked, but not very extensive. In all cases the walls of the blood-vessels seemed to be thickened. The cellularity was of the young connective tissue and lymphoid cell types.

Another series consisting of seven guinea-pigs were injected subcutaneously with varying doses of potassium bichromate in a 1 and a 5 per cent. aqueous solution.

Guinea-Pigs 136 and 137, weights 475 and 490 gm., were injected subcutaneously with 2 minims of a 5 per cent. solution of potassium bichromate. The former died four days and the latter twelve days after the injection. At autopsy no pathological lesion was noted. Microscopically both guinea-pigs showed a similar lesion of the myocardium. There was marked congestion and a slight diffuse young connective tissue and lymphoid cellularity, which was most marked about the walls of the blood-vessels. There were areas where the muscle appeared hypertrophied and other areas where it is degenerated, the muscle cells having

swollen and faintly stained nuclei. The walls of the blood-vessels were thickened, and infiltrated with young connective tissue cells, and the cells of the intima appeared to be proliferating.

The remaining five guinea-pigs of this series although they received different amounts of the potassium bichromate and at different intervals, all showed a similar lesion and consequently all will be taken together.

Guinea-Pig 179, weight 480 gm., was injected subcutaneously with 2 minims of a 1 per cent. solution of potassium bichromate. This was repeated three days later, again in five days and nine days. Eleven days later the dose was increased to four minims, and two days after this to 8 minims, which was repeated four times at weekly periods and four more times at three-week intervals. Thus the guinea-pig received four 2-minim doses, one 4-minim and nine 8-minim injections. The guinea-pig was killed ten days after the last injection. Guinea-Pig 180, weight 465 gm., was injected similarly, including the second 8-minim dose, after which it died. Guinea-Pig 181, weight 835 gm., was injected subcutaneously with 2 minims of a 5 per cent. solution of potassium bichromate, and this was repeated six days later, and again nine days later. On the eleventh day, that is, two days after the last injection, the amount of potassium bichromate was changed to 5 minims of a 1 per cent. solution and this was injected twice with two days intervening. Two days later again the dose of potassium bichromate was increased, this time to 15 minims of a 1 per cent. solution, and was injected six times at weekly intervals and three times at three-week intervals. The guinea-pig was killed eight weeks after the last injection. Guinea-Pig 183, weight 400 gm., was injected subcutaneously with 5 minims of a 1 per cent. solution of potassium bichromate three times in ten days. After this the amount of bichromate was increased to 8 minims of the 1 per cent. solution and was injected subcutaneously eight times at weekly periods and two times at three-week intervals. The guinea-pig was killed ten days after the last injection. Guinea-Pig 184, weight 390 gm., was injected subcutaneously with 1 minim of a 1 per cent. solution of potassium bichromate six times in twelve days and with 8 minims of a 1 per cent. solution two times in three weeks. The guinea-pig died one day after the last injection. At autopsy none of these guinea-pigs showed a pathological lesion of the heart. Microscopically they all showed a very similar lesion of the myocardium. There was marked congestion and a slight diffuse cellularity of the young connective tissue and lymphoid cell types. Also these cells appeared in rather extensive foci, and were more noticeable about the blood-vessels. The walls of the blood vessels were thickened and were infiltrated with the same types of cells. In Guinea-Pigs 180 and 184 this cellularity was less marked than in the two other guinea-pigs.

This series showed a rather more marked cellularity of the myocardium than any previous series, although the lesion in none of these guinea-pigs was very extensive or destructive.

The last series consisted of seventeen rabbits of varying weights injected subcutaneously with varying amounts of potassium bichromate in an aqueous solution at varying intervals.

Rabbits 131 and 133, each weighing 1900 gm., were injected subcutaneously with 1 c.c. of a 5 per cent. solution of potassium bichromate, and they died five and six days later, respectively. At autopsy no pathological lesion was found. Microscopically the myocardium of Rabbit 131 showed a very slight cellularity of the young connective tissue and lymphoid cell types diffusely and in foci. The walls of the blood-vessels were slightly thickened and infiltrated with young connective tissue cells. Rabbit 133 showed a similar picture in the myocardium, except that there was in addition congestion and plasma cells in the foci and more degeneration of the muscle cells which had lost the cross-striations.

Rabbit 125, weight 1200 gm., was injected subcutaneously with 1 c.c. of a 5 per cent. solution of potassium bichromate, the injection being repeated on the following day. The rabbit died on the third day. Nothing pathological was noted at autopsy. Microscopically there were areas of old fibrous tissue infiltrated with young connective tissue cells, also foci of these young cells which replaced the muscle cells.

Rabbit 182, weight 2170 gm., was injected subcutaneously with 0.75 c.c. of a 5 per cent. solution of potassium bichromate. The rabbit died two weeks later. At autopsy nothing pathological was noted. Microscopically there was congestion and numerous and extensive foci of young connective tissue cells with fibrils, lymphoid cells and a very few leukocytes.

Rabbits 134 and 135, weighing 1840 and 1880 gm., were each injected subcutaneously with 0.5 c.c. of a 5 per cent. solution of potassium bichromate. This was repeated eight days later, and thereafter 21 minims of a 1 per cent. solution of potassium bichromate was injected subcutaneously at three-week intervals for four injections. Both were killed eight weeks after the last injection. At autopsy nothing pathological was found. Microscopically both rabbits showed a similar lesion of the myocardium. There was a slight diffuse young connective tissue and lymphoid cell increase with moderate congestion. In addition, there were foci of young connective tissue, lymphoid cells, and plasma cells. These foci were quite extensive, and replaced the muscle cells. The myocardium of Rabbit 135 had a slightly more extensive lesion than did Rabbit 134. In both the walls of the blood-vessels were thickened.

Rabbits 222, 223, 224, 225, and 231, weighing respectively 1300, 1530, 1730, 1700, and 1330 gm., were each injected subcutaneously with 21 minims of a 1 per cent. solution of potassium bichromate. This was repeated every three weeks for four more injections. The rabbits were killed respectively ten, three, ten, nine and eight weeks after the last injection. At autopsy only Rabbit 225 showed a pathological change, and this was a straw-colored fluid in the abdominal cavity. Microscopically Rabbits 222, 224, and 225 had a similar lesion of the myocardium. This was a slight diffuse young connective tissue cellularity and also foci of these cells with fibrils scattered throughout the myocardium with more or less replacement of the muscle cells by these foci. The walls of the blood-vessels were thickened. The other two rabbits, Nos. 223 and 231, showed only a very slight diffuse young connective tissue cellularity of the myocardium.

Rabbits 244, 245, 257, and 258, weighing respectively 2380, 2050, 2330 and 3310 gm., were each injected subcutaneously with 21 minims of a 1 per cent. solution of potassium bichromate four times at three-week intervals. The rabbits were killed eight, one, five, and nine weeks respectively after the last injection. At autopsy the only pathological lesion found was in Rabbit 245, whose aorta was stiffened and sclerosed. In Rabbit 257 the visceral pericardium was covered with a very slight fibrinous film, and the heart of Rabbit 258 was large. Microscopically the myocardium of Rabbit 244 showed no lesion. The myocardium of Rabbit 245 showed a slight diffuse young connective tissue and lymphoid cellularity. In addition in the center of the myocardium of the left ventricle there was an area of young fibrous tissue invading and replacing the muscle. The walls of the blood-vessels were infiltrated with young connective tissue cells. The myocardium of Rabbits 257 and 258 showed a very slight diffuse young connective tissue cellularity, with a very few lymphoid cells.

Rabbit 228, weight 1310 gm., was injected subcutaneously with 21 minims of a 1 per cent. solution of potassium bichromate three times at three-week intervals, and the rabbit died three days after the last injection. At autopsy there was considerable blood-stained fluid in the abdominal cavity. Microscopically the myocardium showed an increased cellularity of the young connective tissue and lymphoid types, both in foci and diffusely.

Rabbits 262 and 263, weights 1550 and 2000 gm., were each injected subcutaneously with 21 minims of a 1 per cent. solution of potassium bichromate twice with three weeks intervening between the two injections. The rabbits were killed

eleven and twelve weeks after the last injection. At autopsy no pathological lesion was found. Microscopically the myocardium of each rabbit showed small clumps or beginning foci of young connective tissue and lymphoid cells.

As did the previous series, this series showed a slight cellularity of the young connective tissue and lymphoid cell types in foci and diffusely. In no rabbit was the lesion at all extensive.

Summary

Although practically all these animals showed a more or less increased cellularity of the myocardium, it was extremely slight in many, and in no animal was the cellularity marked. Whereas, in the series in which spartein sulphate and adrenalin chlorid were used intravenously and in which the spartein was injected subcutaneously followed intravenously by adrenalin, all the rabbits showed a considerable increased cellularity, and in some there was a considerable connective tissue proliferation. Also the extent of the lesion was in proportion to the number of injections in the spartein series. But in the series just described in this paper the number of injections seemed to play a small part in the extensiveness of the lesion.

Carney Hospital.

STUDY XIV. PERICARDIAL LESIONS PRODUCED BY RENAL IRRITANTS (URANIUM NITRATE, ARSENIC AND POTASSIUM BICHROMATE)*

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During the past winter, 1910, Dr. R. M. Smith, at the suggestion and under the supervision of Dr. H. A. Christian, did some experimental work on chronic nephritis. The drugs used were an aqueous solution of uranium nitrate, arsenic in the form of Fowler's solution, and potassium bichromate in aqueous solution. These drugs were used subcutaneously in various doses and at various intervals, and in addition, the arsenic was given by stomach tube. The majority of animals used were rabbits, and a few guinea-pigs. For a more detailed description and the results obtained I refer to Dr. Smith's paper. The work was carried on in the Department of Theory and Practice of Physic at the Harvard Medical School. This paper is a description of the lesions of the pericardia that occurred in Dr. Smith's experiments, and these may be considered a control to the experiments in which spartein sulphate and adrenalin chlorid were used to produce pericarditis.

One series of thirteen rabbits of varying weights were injected subcutaneously with 0.001 gm. and 0.002 gm. of uranium nitrate at various intervals.

*This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

*Reported at the Annual Meeting of the Association of American Physicians, May 3-5, 1910, Washington, D. C.

In this series, although all the rabbits showed either an acute or a chronic lesion of the kidneys, none showed any lesion of the pericardium.

Another series of twenty-one rabbits of varying weights were injected subcutaneously with 0.005 gm. of uranium nitrate at three-week intervals, which interval was found to produce the most satisfactory kidney lesion. In this series thirteen rabbits showed no lesion of the pericardium, whereas eight rabbits did have a lesion of the pericardium although it was not marked.

Rabbits 198, 199 and 200, weighing respectively 1190, 1140, and 1190 gm., were injected subcutaneously with 0.005 gm. of uranium nitrate, and all died five days after injection. Macroscopically, no lesion of the pericardium could be made out. Microscopically their pericardia showed congestion which was more marked in some places than in others.

Rabbit 251, weight 1690 gm., was injected once in the same manner with the same drug, and it died seven days later. Macroscopically there was no lesion, but microscopically the pericardium showed slight infiltration with young connective tissue and lymphoid cells.

Rabbits 194, weight 1280 gm., 195, weight 1170 gm., and 196, weight 1215 gm., were injected subcutaneously with 0.005 gm. of uranium nitrate, and this was repeated at three-week intervals for six times more, the rabbits being killed four and six weeks after the last injection. Macroscopically there was no pericardial lesion. Microscopically Rabbits 194 and 195 showed a slight increased cellularity of the young connective tissue and lymphoid cell types. Rabbit 196, microscopically, showed a slight increased cellularity throughout the pericardium, like the two former rabbits and in addition the pericardium at the base of the left ventricle was rather markedly infiltrated with lymphoid cells and young connective tissue, which in one place extended down into the subpericardial myocardium to form a fairly large patch of loose fibrous tissue infiltrated with young connective tissue and lymphoid cells with a few red blood-cells and leukocytes. The muscle is degenerated and is replaced by this patch of tissue.

Rabbit 178, weight 1580 gm., was injected subcutaneously six times at three-week periods with 0.005 gm. of uranium nitrate, and was killed nine weeks after the last injection. Macroscopically the pericardium showed no lesion. Microscopically there was a slight increase of young connective tissue cells with increased vascularity at the juncture of the pericardium and the myocardium.

The remaining rabbits of this series showed no lesion of their pericardia.

Thus it is seen that of twenty-one rabbits all injected similarly, and all of which showed either acute or chronic lesions of both of their kidneys, only eight rabbits had a lesion of their pericardium, and this lesion was only slight in each rabbit, and it was not confined to any special number of injections or to any special time limit, although four of the rabbits showing a lesion, namely, congestion only, received only one injection and died a few days later. The other four rabbits having a lesion of the pericardium were injected six and seven times, and this lesion was only a slight increased cellularity of the young connective tissue and lymphoid cell types.

In a third series guinea-pigs of varying weights were injected subcutaneously with varying doses of uranium nitrate at varying intervals of

time. In all, ten guinea-pigs were used and all showed a more or less marked lesion of their pericardia microscopically, but nothing macroscopically.

Guinea-Pig 175, weight 475 gm., was injected subcutaneously with 0.001 gm. of uranium nitrate, and died four weeks later. Microscopically there was proliferation of the pericardial cells.

Guinea-Pigs 140, weight 440 gm., 186, weight 390 gm., and 176, weight 550 gm., were all injected subcutaneously with 0.001 gm. of uranium nitrate, which was repeated at three-week intervals for eight, five and six times in each rabbit respectively. Guinea-Pig 140, receiving eight injections, and killed ten days after the last injection, showed foci of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium. In Guinea-Pig 186, which was injected five times, and died ten days after the last injection, the pericardium showed moderate congestion and a fairly marked increase of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium. Guinea-Pig 176 received six injections and was killed ten days after the last injection. There was a slight young connective tissue and lymphoid cell increase.

Guinea-Pigs 139, weight 685 gm., and 142, weight 560 gm., were injected subcutaneously with 0.0005 gm. of uranium nitrate every other day for ten injections, and after this the uranium was increased to 0.001 gm. Guinea-Pig 142 died three weeks later, and the pericardium was slightly thickened with some young connective tissue cell increase, a few plasma cells, and a few red blood cells also were present. The other, Guinea-Pig 139, survived eight injections of 0.001 gm. at three-week intervals, and was killed ten days after the eighth injection. The pericardium showed only congestion and edema.

Guinea-Pigs 229, weight 400 gm., and 241, weight 485 grams, were injected subcutaneously with 0.001 gm. of uranium nitrate, which was repeated in 229 for three times and the animal was killed five weeks after the fourth injection. In Guinea-Pig 241 the drug was repeated four times, when the animal died four days after the fifth injection. In Guinea-Pig 229 the pericardium was slightly thickened with an increase in the young connective tissue and lymphoid cells, and in addition, a few plasma cells were present. Guinea-Pig 241 showed the same kind of cells, but in foci scattered throughout the pericardium.

Guinea-Pig 185, weight 670 gm., was injected subcutaneously with 0.002 gm. of uranium nitrate, repeated five times at three-week intervals, and was killed ten days after the sixth injection. There was quite marked congestion of the pericardium, and marked young connective tissue and lymphoid cell increase at the juncture of the pericardium and the myocardium.

Guinea-Pig 188, weight 450 gm., was injected subcutaneously with 0.003 gm. of uranium nitrate, and died six days later, showing thickening of the pericardium in places where there was considerable young connective tissue and lymphoid cell increase with numerous plasma cells.

The guinea-pigs which got a slightly larger dose of uranium nitrate in proportion to weight than the rabbits showed a slightly more marked lesion and this lesion was more constant.

A series of rabbits, fourteen in all, were experimented on with arsenic in the form of Fowler's solution. Three rabbits received the arsenic by stomach-tube, a dose of 8 or 10 minims in as much water. Two rabbits were injected subcutaneously several times, and afterward it was given by stomach tube. Nine rabbits were injected subcutaneously only, the subcutaneous dose in all rabbits being 10 minims undiluted, with the exception of one rabbit, which got 8 minims.

Rabbit 243, weight 2280 gm., was injected subcutaneously with 10 minims of Fowler's solution. This was repeated at seven-day intervals between the doses for two times, and the rabbit died two days after the last or third injection. At autopsy the pericardium was filled with a colorless fluid. Nothing was made out macroscopically. Microscopically there were areas of marked congestion, and an occasional lymphoid and young connective tissue cell.

Rabbit 239, weight 2250 gm., was injected subcutaneously with 10 minims of Fowler's solution for four times, with seven-day intervals between the injections. This rabbit died seven days after the last injection. There was nothing abnormal macroscopically. Microscopically there was very slight young connective tissue and plasma cell infiltration with slight congestion and edema of the pericardium.

Rabbits 254, weight 1950 gm., and 255, weight 2180 gm., were injected subcutaneously with 10 minims of Fowler's solution at ten-day intervals. Each rabbit received seven injections. The former died two days after the last injection, the latter was killed six weeks later. Microscopically the pericardium of Rabbit 254 showed only an extremely slight young connective tissue cell increase. In the latter, 255, there was marked congestion of the pericardium.

Rabbit 233, weight 1600 gm., was injected subcutaneously with 8 minims of Fowler's solution ten times, with seven or ten days between the injections, and was killed six weeks after the last injection. Microscopically at the juncture of the pericardium and the myocardium there was a slight infiltration with young connective tissue and lymphoid cells.

Rabbits 234, weight 2470 gm., and 237, weight 1950 gm., were injected subcutaneously with 10 minims of Fowler's solution for ten injections at seven- or ten-day intervals, extending over a period of three months. The former was killed six weeks and the latter eight weeks after the last injection. In both, microscopically, there were foci of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium.

Rabbits 235, 236, and 238, weighing respectively 2520, 1920 and 1730 gm., were all given Fowler's solution by stomach-tube. Rabbit 235 received 10 minims in an equal amount of water, and Rabbits 236 and 238 got 8 minims with 10 minims of water. They all received ten doses at seven-day intervals and were killed nine weeks, six weeks, and eight weeks respectively after the last or tenth dose. Nothing abnormal was found macroscopically. Microscopically there were foci of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium. Rabbit 238 showed a less marked picture and Rabbit 236 showed slight congestion also.

Rabbit 138, weight 2730 gm., was injected subcutaneously with 10 minims of Fowler's solution, and this was repeated two days later. For the next succeeding twenty days the rabbit was given a rest, because the urine showed that the rabbit had a severe acute nephritis. On the twenty-first day after the last or second subcutaneous injection, the rabbit was given 10 minims of Fowler's solution, plus 10 minims of water by stomach-tube, and this was repeated twice at three-day intervals. The stomach-tube was used in this case rather than continuing subcutaneous injections, because there was a wide area of necrosis and sloughing of the abdominal wall. It might be stated here that in all the rabbits to which the arsenic was given subcutaneously there was marked necrosis followed by sloughing of the abdominal wall for quite an extensive area about the site of previous injection. This Rabbit 138 died three days after the last dose of Fowler's solution. Microscopically the pericardium was slightly infiltrated with young connective tissue cells and there were areas of marked congestion.

Rabbit 121, weight 2250 gm., was injected subcutaneously with 4 minims of Fowler's solution, this was repeated on the next day, and on the third day the dose was increased to 7 minims, which was repeated on the following day. On the fifth day the dose was increased to 10 minims and this was repeated every day for eleven injections. Thus the rabbit got sixteen injections in as many days. On account of marked sloughing and because the urine gave evidence of a nephritis, injections were suspended for four weeks. At the end of that time

the rabbit was given 10 minims of Fowler's solution by stomach-tube every day for five days. On the sixth day the rabbit died. Microscopically there was mild congestion of the pericardium and areas of hemorrhage at the juncture of the pericardium and the myocardium.

Rabbit 132, weight 2050 gm., was injected subcutaneously with 10 minims of Fowler's solution seven times in ten days, when the rabbit died. The pericardium showed no lesion either macroscopically or microscopically.

Rabbit 253, weight 2250 gm., was injected subcutaneously with ten minims of Fowler's solution at seven- and ten-day intervals for seven times and was killed eight weeks after the last injection. The pericardium was not abnormal.

Therefore, of the fourteen rabbits which were given arsenic in various ways over long and short periods, two showed no lesion of the pericardium, two others only congestion, four showed a very slight cellular increase, which was hardly more than normal, and six rabbits did have a slightly increased cellularity of the pericardium.

A fifth series of seven guinea-pigs of varying weights were injected subcutaneously at various intervals with varying doses of an aqueous solution of potassium bichromate.

Guinea-Pigs 136 and 137, weighing respectively 475 and 490 gm., were injected subcutaneously with 2 minims of a 5 per cent. solution of potassium bichromate. The former, Guinea-Pig 136, died four days and the latter died twelve days after the injection. Macroscopically the pericardium appeared normal. Microscopically, the pericardium of Guinea-Pig 136 showed areas of young connective tissue and lymphoid cells with congestion. In Guinea-Pig 137 there was a very slight young connective tissue and lymphoid cell infiltration both diffusely situated in the pericardium.

Guinea-Pig 179, weight 480 gm., was injected subcutaneously with 2 minims of a 1 per cent. solution of potassium bichromate and this was repeated three, five, and nine days later. On the eleventh day the dose was increased to 4 minims of the 1 per cent. solution, and on the thirteenth day again the dose was increased to 8 minims of the 1 per cent. solution and the guinea-pig was injected as previously. This same dose was repeated five times at three-week intervals and three times at weekly periods. Thus the guinea-pig was injected subcutaneously fourteen times, four times with 2 minims, once with 4 minims, and nine times with 8 minims of a 1 per cent. solution of potassium bichromate in four and one-half months. The guinea-pig was killed ten days after the last injection. Microscopically the pericardium was a little thickened with an increase of young connective tissue and lymphoid cells with congestion and edema.

Guinea-Pig 180, weight 465 gm., was injected exactly the same as No. 179, except that it survived only two injections of the 8-minim dose and died two weeks after the last or seventh injection, thus receiving mostly small doses. Microscopically the pericardium showed a similar picture to Guinea-Pig 179.

Guinea-Pig 187, weight 835 gm., was injected subcutaneously with 2 minims of a 5 per cent. solution of potassium bichromate, and six days later with 5 minims of a 1 per cent. solution. This was repeated in three days and again in two days later. After this the dose was increased to 8 minims and the guinea-pig was thusly injected. Two days later the dose was again increased to 15 minims of a 1 per cent. solution and the guinea-pig was injected and this injection was repeated six times at weekly intervals and twice more at three-week intervals. Eight weeks after the last or thirteenth injection the guinea-pig was killed. Microscopically at the base of the left auricle the pericardium was much thickened with young connective tissue and lymphoid cell infiltration, congestion, edema and increased vascularity.

Guinea-Pig 183, weight 400 gm., was injected subcutaneously with 5 minims of a 1 per cent. solution of potassium bichromate. This was repeated in six days, again in two days, and two days later the dose was increased to 8 minims and the guinea-pig was injected. After this the injections were suspended for six weeks, and then the guinea-pig was again injected subcutaneously at weekly intervals with 8 minims of a 1 per cent. solution for seven times. The guinea-pig was killed ten days after the last injection. Microscopically there was a slight increase of young connective tissue cells and slight congestion of the pericardium.

Guinea-Pig 184, weight 390 gm., was injected subcutaneously with 1 minim of a 1 per cent. solution of potassium bichromate, and this was repeated every other day for six times, then the dose was increased to 8 minims of the 1 per cent. solution, and the guinea-pig was thus injected two days later, and repeated in two weeks. The animal died the following day. Microscopically the pericardium showed considerable increase of young connective tissue and lymphoid cells.

Thus of the seven guinea-pigs which were injected subcutaneously with various amounts of potassium bichromate at various intervals, all showed some lesion of the pericardium, but in none was the lesion extensive or marked, usually only a slight increased cellularity being noted.

The last series consists of eighteen rabbits injected subcutaneously with potassium bichromate in doses of 21 minims of a 1 per cent. solution at three-week intervals; this method seemed to give the best kidney lesion. A few rabbits, however, received smaller doses of a 5 per cent. solution.

Rabbits 222, 223, 224, 225, and 231, weighing respectively 1300, 1530, 1730, 1700 and 1330 gm., were all injected subcutaneously on the same dates with 21 minims of a 1 per cent. solution of potassium bichromate. Each rabbit was injected five times at three-week intervals and they were killed respectively ten, three, ten, nine, and eight weeks after the last injection. Microscopically nothing abnormal was noted. Microscopically Rabbits 222 and 225 both showed slight young connective tissue and lymphoid cell increase at the juncture of the pericardium and the myocardium. The pericardium of Rabbit 224 was very slightly infiltrated with young connective tissue cells with congestion. The pericardia of Rabbits 223 and 231 were not abnormal.

Rabbits 224, weight 2380 gm., 245, weight 2050 gm., 257, weight 2330 gm., and 258, weight 3310 gm., were all injected subcutaneously on the same dates with 21 minims of a 1 per cent. solution of potassium bichromate. In all, each rabbit received four injections at three-week intervals, and they were killed eight, eight, five and nine weeks respectively after the last injection. Macroscopically the pericardia were normal, and microscopically no lesion could be made out with the exception of Rabbit 244, whose pericardium showed a very slight young connective tissue cell infiltration with congestion.

Rabbits 262 and 263, weighing 1550 and 2000 gm., were injected with 21 minims of a 1 per cent. solution of potassium bichromate two times with three weeks' interval between, and the rabbits were killed twelve weeks later. Macroscopically the pericardia of both were normal. Microscopically Rabbit 262 showed no lesion of the pericardium, but Rabbit 263 showed a slight young connective tissue and lymphoid cell infiltration at the juncture of the pericardium and the myocardium.

Rabbit 228, weight 1310 gm., was injected like the above for three times, and died three days after the last injection. Microscopically the pericardium was very slightly infiltrated with young connective tissue cells and slight congestion was present.

Rabbits 134, weight 1840 gm., and 135, weight 1880 gm., were injected subcutaneously with 0.5 c.c. of a 5 per cent. solution of potassium bichromate. Ten days later Rabbit 134 was injected with 0.25 c.c. and Rabbit 135 was injected

with 0.5 c.c. of the same solution. After this 21 minims of a 1 per cent. solution were injected subcutaneously at three-week intervals for four times. Both rabbits were killed eight weeks after the last injection. Their pericardia were not abnormal macroscopically. Microscopically there was a very slight diffuse increase of young connective tissue cells and also foci of these cells, both types of lesion being situated at the juncture of the pericardium and the myocardium.

Rabbits 131 and 133, each weighing 1900 gm., were injected subcutaneously with 1 c.c. of a 5 per cent. solution of potassium bichromate. The former died five days and the latter six days after the injection. Microscopically Rabbit 131 showed a very slight young connective tissue and lymphoid cell infiltration at the juncture of the pericardium and myocardium. Rabbit 133, microscopically, showed proliferation of the pericardial cells, occasional foci of young connective tissue and lymphoid cells and areas of hemorrhage and edema at the juncture of the pericardium and the myocardium.

Rabbit 182, weight 2170 gm., was injected subcutaneously with 0.75 c.c. of a 5 per cent. solution of potassium bichromate, and the rabbit died fourteen days later. Microscopically there were foci of young connective tissue and lymphoid cells at the juncture of the pericardium and the myocardium.

In this series of eighteen rabbits six showed no lesion of the pericardium, in six there was a slight increased cellularity, and in the remaining six rabbits the pericardium showed a fairly marked cellularity.

Summary

Thus it is seen that the drugs used in these experiments, although in all cases there was a nephritis more or less marked, produced in no case a marked lesion of the pericardium, and in most animals there was only a slight deviation from the normal, and many showed no lesion at all; whereas, in the experiments with spartein sulphate and adrenalin chlorid, both injected intravenously, and in those where the spartein sulphate was used subcutaneously, followed by adrenalin intravenously, practically all rabbits showed a considerable and many showed a marked lesion of the pericardium.

Carney Hospital.

STUDY XV. HEPATIC LESIONS ASSOCIATED WITH EXPERIMENTAL CARDIAC LESIONS

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In a study of experimental myocarditis produced by spartein sulphate and adrenalin chlorid carried on in this laboratory by Walker, fifty-seven rabbits received injections of these substances in varying dosage. The livers from these rabbits form the basis of this study.

The most striking thing in this series is the infrequency of hepatic lesions, in sharp contrast to the very constant cardiac lesions. Spartein and adrenalin appear to produce very slight direct change in the liver, at most as demonstrable in our animals, a transient congestion of the liver (active hyperemia) as shown in Figure 32* from a rabbit (Rabbit

*All photographs for this series of articles were made by Mr. L. L. Brown, of the Massachusetts General Hospital, for whose careful work I wish to express my thanks.

273[38]) dying shortly after receiving subcutaneously 0.025 gm. spartein sulphate followed intravenously by 0.2 c.c. of a 1 to 1,000 solution of adrenalin chlorid. On the other hand in some rabbits there result hepatic changes which are indirectly caused by the spartein and adrenalin in the sense that these substances produce cardiac lesions and consequent to those passive congestion of the liver arises. Thus we have an experimental method of producing the hepatic lesions of chronic passive congestion in which the conditions are quite analogous to those found in man suffering from cardiac insufficiency. Unfortunately in only a few of these rabbits did the cardiac lesion advance to a stage of moderate decompensation, and only six showed hepatic changes interpretable as the consequence of passive congestion. However, these changes are in harmony with the views recently expressed by Mallory[39] in regard to the histogenesis of the hepatic lesions of chronic passive congestion, views contrary to those generally held by pathologists, and are described here mainly for that reason.

In five livers (Rabbits 266, 275, 280, 282, 283) the lesion present consists merely in a dilatation of the sinusoids, most marked in the vicinity of the central veins (terminal branches of the hepatic vein) and this dilatation is quite generally present throughout the liver. Figures 33 and 34 show this dilatation in contrast to the normal condition shown in Figure 35. Along with the dilatation of the sinusoids the liver cells show a moderate decrease in diameter. No other changes are found in these livers. The amount of dilatation varies in the several livers and in none is it extreme. This change appears to be a simple passive congestion of the liver consequent to the cardiac lesion.

In a fifth rabbit (Rabbit 79) of this series a very different hepatic lesion occurs. In the first place there is only moderate dilatation of the sinusoids, not very general in its distribution. This is notwithstanding the fact that a marked cardiac lesion existed and the heart functionally was decompensated as evidenced by a marked degree of edema and ascites. In the second place there is a very marked lesion distinctly irregular in its distribution consisting of the disappearance of liver cells and their replacement by blood corpuscles. This lesion corresponds in appearance with what is seen in the liver lobules of marked degrees of chronic passive congestion in man, a picture usually explained as arising from the atrophy and disappearance of liver cells and their replacement by dilated sinusoids. Figures 36, 37 and 38 show these lesions under moderate magnification and illustrate their focal character. More careful study of the changes in the liver of this rabbit shows that these lesions are irregularly distributed, being much more numerous in some sections than in others taken from different parts of the liver; however, as some

38. For protocols of rabbits referred to, see end of this paper.
39. Mallory: Journal Med. Research, 1911, new series, xix, 455.

evidence of this change is found in all sections, the lesion is widely distributed. Their size varies from a small focus to an area occupying more than half the field of a Zeiss 16 mm. objective with No. 4 ocular. The lesion nearly always is closely adjacent to some branch of the hepatic vein, and very rarely extends peripherally so as to be in contact with branches of the portal vein. This distribution of lesion corresponds closely with that of extensive central necroses in human livers as described by Mallory[40] and is almost identical with the distribution of typical liver necroses of this type found in one rabbit (No. 293) of this series in which there was no vascular or other lesion. In its most typical form the lesion consists of an area from whose center liver cells have entirely disappeared and there remain only red blood corpuscles, a small amount of hepatic reticulum and blood-vessel walls with connective tissue and endothelial cells. In the peripheral portion of such an area liver cells are found in different stages of degeneration. Many of these cells are more or less necrotic. The necrosis is evidenced by the cytoplasm staining pinkish to dark pink in contrast to the blue of the normal cytoplasm. The cytoplasm usually contains fine granules of yellowish pigment and the cells are smaller than the normal liver cell. The nuclei in some cells have disappeared, but as a rule the nuclei show much less change than does the cytoplasm. Almost always hemorrhage has taken place about the liver cells (Figure 39), and this is particularly well shown in sections stained by Mallory's anilin blue connective tissue stain where the blood corpuscles are plainly seen between the liver cell and the wall of the sinusoid (Figure 40). Polynuclear leukocytes to a slight extent wander into the space about the necrotic liver cells or penetrate them. At the periphery of many of these lesions transitions can be traced between slightly changed liver cells with a few red blood corpuscles about them to spaces from which liver cells have disappeared entirely, and their place has been taken by red blood corpuscles. In sections stained with the anilin blue connective tissue stain, foci where no liver cells appear can be seen to be made up very largely of red blood corpuscles filling spaces formerly occupied by hepatic cells, and in such areas the dilated sinusoid makes but a small part of the blood lake. In other places hemorrhage into pericellular spaces has taken place though the hepatic cells show very slight evidence of degeneration beyond atrophy and a changed granularity indicating some disturbance in the usual cytoplasmic architecture.

Scattered through the sections are groups of liver cells, almost always at the periphery of hemorrhagic foci such as are described above, which present a very different appearance from the cells showing necrosis. These cells have undergone a vacuolar change. They are very much swollen (Figure 41); their nuclei, centrally situated, stain quite well; in place of the usual granular cytoplasm there often remains only a few scattered

40. Mallory: Jour. Med. Research, 1901, vi, 264.

cytoplasmic granules and threads; some cells have a distinctly punched-out appearance as if all else than nucleus and cell membrane had disappeared; other cells have a distinct foam structure made up of medium-sized vacuoles. The exact relation of these liver cells to the hemorrhagic foci is not clear. The line of demarcation between hemorrhagic focus and vacuolar cells is usually sharp, but the two are ordinarily closely related. Sometimes sinusoids between the vacuolated cells are dilated, usually not. In a few places red blood corpuscles appear to have penetrated the cell membrane and are crowded about the nucleus. Possibly to a certain extent hemorrhagic foci form as a sequence of this type of cell degeneration. However, this cannot be said to be proved by the findings in this liver.

In addition to the changes already described only one other liver of the series showed a lesion; that was a fairly well-marked cirrhosis probably not associated with the spartein and adrenalin in a causative way, as it was quite similar to a type of cirrhosis occasionally met with in rabbits, either treated in various ways, or killed without any treatment for controls, and so presumably a spontaneous or accidental lesion.

Summary

In a series of fifty-seven rabbits treated in various ways with spartein and adrenalin, very few hepatic lesions were found. In one focal necroses and in another cirrhotic changes were encountered, not believed to be associated with the drugs in a causative sense. In animals killed shortly after injections of larger doses of spartein and adrenalin acute hyperemia of the liver is found. In rabbits showing distinct cardiac lesions, two changes are found in the liver. One is a simple general dilatation of the central sinusoids with slight atrophy of liver cells, simple passive congestion, a mechanical effect. The other is a focal lesion with partial disappearance of liver cells and their replacement by blood. The latter change is the result of simple passive congestion combined with degeneration, mainly necrosis of liver cells as shown by the irregular distribution of the lesion and the presence of blood outside the sinusoids, either about degenerated liver cells or occupying the space remaining after the total disappearance of the liver cells, simple passive congestion plus focal liver degeneration, a mechanical effect in combination with a toxin of some kind producing cell injury and interstitial hemorrhage.

PROTOCOLS OF RABBITS REFERRED TO IN THE PAPER

PROTOCOL 79.—Rabbit. Weight 1700 gm. December 12, 1908, spartein sulphate 0.021 gm., adrenalin chlorid 0.2 c.c., both subcutaneously. January 25, same. February 19, spartein sulphate 0.021 gm., adrenalin chlorid 0.26 c.c., March 16, same. April 9, weight 2100 gm. Spartein sulphate 0.025 gm. subcutaneously, adrenalin chlorid 0.2 c.c. intravenously. Killed April 24, 1909. Weight 2280 gm.

Autopsy.—There is definite, well-marked edema of the subcutaneous tissue and the scrotum. The peritoneum contains 115 c.c. of fluid with a specific gravity of 1018. Liver, weight 102 gm., appears very large. Its surface is mottled in

color, being dark red, checkered over with a tracery of lighter grayish red areas corresponding apparently to lobules and giving the appearance of a nutmeg liver. Pleural cavities are filled with fluid. Heart, right ventricle is of normal consistence, as is the right auricle. The left auricle is distinctly thickened, feels firmer than right. The left ventricle from a point a little below the auriculo-ventricular groove almost down to the apex feels dense, the wall is thickened and is paler in color than other parts of the heart. Lungs, reddish pink, exuding a considerable amount of frothy serum from the cut surface.

PROTOCOL 266.—Rabbit. December 7, 1909, spartein sulphate 0.025 gm. intravenously, adrenalin chlorid 0.2 c.c. intravenously. December 9, spartein sulphate 0.025 gm., adrenalin chlorid 0.2 c.c., both intravenously. December 13, 16, 20, January 5, same. January 10, spartein sulphate 0.018 gm., adrenalin chlorid 0.2 c.c., both intravenously. January 13, spartein sulphate 0.0125 gm., adrenalin chlorid 0.2 c.c., both intravenously. Died January 13. Weight 1420 gm.

Autopsy.—No free fluid in the cavities except small amount of muddy fluid in the pericardium. Quite firm fibrous adhesions between the two layers of the pericardium. Heart appears large, weight, 6.05 gm., surface rough from torn adhesions. Kidneys, weight, 9.55 gm., on section show a narrow whitish cortex with prominent glomeruli, while the medulla is of a dark brownish color.

PROTOCOL 273.—Rabbit. December 24, 1909, spartein sulphate 0.025 gm. subcutaneously, adrenalin chlorid 0.2 c.c. intravenously. Died December 24. Weight 2170 gm.

Autopsy.—No free fluid in the cavities of organs injected. Heart, weight, 7.5 gm. Kidneys, weight 13.3 gm.

PROTOCOL 275.—Rabbit. December 24, 1909, spartein sulphate 0.025 gm. subcutaneously, adrenalin chlorid 0.2 c.c. intravenously. Died in 15 minutes.

Autopsy.—Much free fluid in the abdominal cavity. Heart, weight, 8.1 gm. Kidneys, weight, 13.3 gm.

PROTOCOL 280.—Rabbit. January 5, 1910, spartein sulphate 0.03 gm., adrenalin chlorid 0.2 c.c., both intravenously. January 10, spartein sulphate 0.018 gm. intravenously. Animal died almost immediately.

Autopsy.—Much free blood-stained fluid in the abdominal, pleural and pericardial cavities. Heart, weight, 7.5 gm. Kidneys, weight, 10.65 gm.

PROTOCOL 282.—Rabbit. January 31, 1910, spartein sulphate 0.007 gm., adrenalin chlorid 0.1 c.c., both intravenously. Repeated Feb. 2, 4, 9, 11, 14, 17, 24. February 28, spartein sulphate 0.008 gm., adrenalin chlorid 0.1 c.c., both intravenously. February 28, spartein sulphate 0.008 gm., adrenalin chlorid 0.1 c.c. March 2, spartein sulphate 0.008 gm., adrenalin chlorid 0.1 c.c. March 5, spartein sulphate 0.008 gm., adrenalin chlorid 0.1 c.c. March 7, spartein sulphate 0.008 gm., adrenalin chlorid 0.1 c.c. March 9, spartein sulphate 0.008 gm., adrenalin chlorid 0.1 c.c. March 12, spartein sulphate 0.008 gm., adrenalin chlorid 0.1 c.c. Same on March 14, all injections intravenously. Died on March 14.

Autopsy.—Slight amount of bloody fluid in abdominal, pleural and pericardial cavities. Heart, weight, 10.1 gm., appears large, left ventricle and auricle very firm and thickened, with a large whitish area near the auriculoventricular groove in the left ventricle. Kidneys, weight 19.1 gm.

PROTOCOL 283.—Rabbit. Spartein sulphate 0.007 gm., adrenalin chlorid 0.1 c.c. Repeated February 2, 4, 9, 11, 14, 17, 24, 28. March 2, spartein sulphate 0.008 gm., adrenalin chlorid 0.1 c.c. Repeated March 5, 7, 9, 12, 14, 16, 19, 21, 23, March 28, spartein sulphate 0.02 gm., adrenalin chlorid 0.1 c.c. Repeated March 31. April 2, spartein sulphate 0.025 gm., adrenalin chlorid 0.165 c.c. Repeated April 4, 6, 9, all injections intravenously. Died April 9.

Autopsy.—Right pleural cavity filled with pus. Upper half of right lung solidified. Pericardium much thickened with adhesions. Heart is enlarged.

PROTOCOL 293.—Rabbit. March 30, spartein sulphate 0.04 gm., adrenalin chlorid 0.2 c.c., both intravenously. Killed March 31.

Autopsy.—Slight amount of straw-colored fluid in the abdominal cavity, considerable amount in pleural cavity. Pericardial cavity filled with bloody fluid.

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A MODIFICATION OF WOHLGEMUTH'S METHOD FOR THE QUANTITATIVE STUDY OF THE ACTIVITY OF THE PANCREATIC FUNCTION *

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The method suggested by Wohlgemuth[1] for the quantitative determination of fecal amylase does not yield dependable data when stools of a pronounced acid reaction are under examination. The principle of Wohlgemuth's method is the extraction of a weighed portion of feces with 1 per cent. sodium chlorid solution and the determination of the amylolytic activity of gradually decreasing volumes of this centrifugated extract, by means of a series of tubes in each of which 5 c.c. of 1 per cent. soluble starch is used as substrate. After twenty-four hours at 38 C. these tubes are treated with a solution of iodin and the extent of digestion determined colorimetrically.

In case the stools do not vary in reaction to any pronounced degree from the normal limits, the above procedure of Wohlgemuth is satisfactory for ordinary clinical purposes. However, when the dietary or metabolic régime of the patient is such as to cause the production of stools which are strongly acid in reaction, the sodium chlorid extracts of such stools will possess such a high acid concentration as to render the interpretation of the findings obtained by means of this method, rather open to question. In a recent investigation as to the influence of water-drinking at meal-time on the activity of the pancreatic function[2] I used Wohlgemuth's method. Certain stools were encountered during the period in which large volumes of water were being daily ingested, which gave evidence of an amylolytic activity several times greater than that possessed by the other stools examined. In searching for an explanation as to this increased starch-hydrolyzing property, I found the stools in question to possess a very strong acid reaction. The question then arose as to the interpretation of the amylolytic power of the feces. Was this increased amylolysis to be interpreted as a sure indication of a stimulated pancreas, or was there a possibility that the acid reaction of the stools had introduced an uncontrolled factor, which vitiated, to a degree, the findings obtained by means of the method in question?

* From the Laboratory of Physiological Chemistry of the University of Illinois.

1. Wohlgemuth: Berl. klin. Wchnschr., 1910, xlvii, 92.
2. Hawk: THE ARCHIVES INT. MED., 1911, viii, 382.

It has been demonstrated that amylase is very susceptible to the influence of acids. For example, Chittenden and Griswold[3] have shown that the presence of a trace of acid will facilitate the action of the enzyme, whereas an acidity but slightly in excess of that bringing about optimum activity of the enzyme will cause absolute inhibition. These findings were verified by Vernon,[4] who also demonstrated the inhibitory influence of alkali. Vernon determined that the enzyme was four times as active in the presence of 0.004 per cent. hydrochloric acid as in a neutral solution and moreover, that an acid concentration of 0.009 per cent. hydrochloric acid entirely inhibited the action of the enzyme. Further tests with organic acids such, for example, as lactic acid and acetic acid, yielded similar findings, it being shown, in general, that traces of organic acids facilitated the action of the enzyme, whereas acid concentrations but slightly in excess of these, caused complete inhibition. The amylase possessed the optimum activity in the presence of 0.0083 per cent. lactic acid. A similar stimulation of amylase activity, through the proper acid concentration, has been demonstrated by Schierbeck,[5] who also determined the retarding action of alkali.

Bearing in mind the facts just cited regarding the influence of acid on the action of amylase, it seemed entirely possible, therefore, in the case of the stools in question in this investigation, that the hydrogen ion concentration of the feces as passed was sufficient to impart to the sodium chlorid extracts, as prepared in the Wohlgemuth technic, the proper hydrogen ion concentration to induce the optimum activity of the amylase. The hydrogen ion concentration of the sodium chlorid extracts of the other stools examined was evidently not sufficient to cause any appreciable augmentation of the enzyme activity above that possessed by the amylase in neutral solution. It is evident, therefore, that only neutralized extracts should be examined, if the application of Wohlgemuth's method is to be of any real service to the clinician and in order to eliminate the question of uncertainty in connection with the interpretation of the data obtained from stools possessing a concentration of H or OH ions, far above the normal limits.

If we attempt to use indicators to determine the neutrality of the fecal extracts, we are at the outset confronted by a serious difficulty. Under all conditions the extracts possess a brownish cast of color, the depth of which depends on the quantity of pigment present. After a series of testings we can, of course, bring the extract to the neutral point, but our testings have been instrumental in removing a certain amount of the fecal extract which has been carried into the indicator paper by capillary attraction. This method of neutralization also causes the fecal

3. Chittenden and Griswold: Am. Chem. Jour., 1881, iii, 305.
4. Vernon: Jour. Physiol., 1901-02, xxvii, 174.
5. Schierbeck: Skandin. Arch. f. Physiol., 1892, iii, 344.

extracts from day to day to assume a variable electrolyte content. This fact of itself would introduce an error, inasmuch as Sherman[6] and collaborators have recently shown that pancreatic amylase is greatly influenced by the electrolyte concentration. Still more recent evidence in this connection has been furnished by Lisbonne[7] and by Gerber.[8] A neutral solution could, of course, be obtained by dialysis, but this manipulation would entail considerable extra labor, and the amylase value of the stools under examination would not be available inside of forty-eight hours from the time they were passed.

The problem was finally solved by the use of a phosphate mixture[9] as the extraction medium.[10] This phosphate mixture contains 0.1 mol dihydrogen sodium phosphate and 0.2 mol disodium hydrogen phosphate per liter. This was prepared in a 1 per cent. solution of sodium chlorid, in order to produce a sufficiently high electrolyte content to insure satisfactory amylolytic action. By the use of this phosphate mixture as an extraction medium, we secure a neutral extract, even though the feces should possess a rather higher H or OH ion concentration than is normally met with.

The action of such a solution, in maintaining a constant hydrogen and hydroxyl ion concentration, is explained by the aid of the ionic theory as follows: Under the conditions outlined above, we have a solution of the two phosphates such that the equilibrium constant

$$k = \frac{(H^+) \cdot (A)}{(HA)}$$

is approximately equal to 1×10^{-7} or to the concentration of the hydrogen ion in pure water, i. e., the solution is neutral. If we add an acid to this solution, then the excess of hydrogen ion derived from the acid will be removed according to the reaction

$$H^+ + A^- = HA$$

and likewise, if we add an alkali the excess of hydroxyl ion will be removed according to the reaction

$$HA + OH^- = H_2O + A^-$$

That is, a mixture of a weak acid and a salt of this acid in the proper proportions will tend to preserve itself in a neutral condition, within certain limits, when treated with varying amounts of acid or alkali. The

6. Sherman, Kendall and Clark: Jour. Am. Chem. Soc., 1910, xxxii, 1073; Sherman and Kendall: Jour. Am. Chem. Soc., 1910, xxxii, 1087.

7. Lisbonne: Compt. rend. Soc. de biol., 1911, lxx, 132.

8. Gerber: Compt. rend. Soc. de biol., 1911, lxx, 391.

Washburn: Jour. Am. Chem. Soc., 1908, xxx, 31; Henderson and Webster: Jour. Med. Research, 1907, New Series, xi, 1; Henderson: Am. Jour. Physiol., 1906, xv, 257; 1908, xxi, 173.

10. I am indebted to Professor E. W. Washburn of the University of Illinois for suggesting the use of this phosphate mixture for this purpose.

mixture of Na_2HPO_4 and NaH_2PO_4 in the proportion 2 to 1, as mentioned above, satisfies the condition as outlined for the preservation of a neutral solution.

If the method described in this paper is followed, the electrolyte concentration of the various fecal extracts will also be very uniform, the only variation being due to any slight variation which may be possessed by the different stools under examination. When it is recalled that only 2 gm. of moist feces are employed, and further that this amount of feces is extracted with a 1 per cent. solution of sodium chlorid containing phosphate as already indicated, it is evident that the variation in the electrolyte concentration of different fecal extracts is entirely negligible.

In harmony with the above facts I would suggest the following modification of Wohlgemuth's method:

Weigh accurately about 2 gm. of fresh feces into a mortar,[11] add 8 c.c. of a phosphate-chlorid solution (0.1 mol dihydrogen sodium phosphate and 0.2 mol disodium hydrogen phosphate per liter of 1 per cent. sodium chlorid), 2 c.c. at a time, rubbing the feces mixture to a homogeneous consistency after each addition of the extraction medium. Permit the mixture to stand at room temperature for a half-hour with frequent stirring. We now have a neutral fecal suspension. Transfer this suspension to a 15 c.c. graduated centrifuge tube being sure to wash the mortar and pestle carefully with the phosphate-chlorid solution and add all washings to the suspension in the centrifuge tube. The suspension is now made up to the 15 c.c. mark with the phosphate-chlorid solution and centrifugated for a fifteen-minute period, or longer if necessary, to secure satisfactory sedimentation. At this point, read and record the height of the sediment column. Remove the supernatant liquid by means of a bent pipette, transfer it to a 50 c.c. volumetric flask and dilute it to the 50 c.c. mark with the phosphate-chlorid solution. Mix the fecal extract thoroughly by shaking and determine its amylolytic activity. For this purpose a series of six graduated tubes is prepared, containing volumes of the extract ranging from 2.5 c.c. to 0.078 c.c. Each of the intermediate tubes in this series will thus contain one-half as much fluid as the preceding tube. Now make the contents of each tube 2.5 c.c. by means of the phosphate-chlorid solution in order to secure a uniform electrolyte concentration. Introduce 5 c.c. of a 1 per cent. soluble starch solution[12] and three drops of toluol into each tube, thoroughly mix the contents by shaking, close the tubes by means of stoppers and place them in an incubator at 38 C. for twenty-four hours. At the end of this time remove the tubes, fill each to within half an inch of the top with ice-water, add one drop of tenth-normal iodin solution, thoroughly mix the contents and examine the tubes carefully with the aid of a strong light. Select the last tube in the series which shows entire absence of blue color, thus indicating that the starch has been completely transformed into dextrin and sugar, and calculate the amylolytic activity on the basis of this dilution. In case of indecision between two tubes, add an extra drop of the iodin solution and observe them again.[13]

11. Duplicate determinations should be made.

12. In preparing the 1 per cent. solution, the weighed starch powder should be dissolved in cold distilled water in a casserole and stirred until a homogeneous suspension is obtained. The mixture should then be heated with constant stirring, until it is clear. This ordinarily takes from eight to ten minutes. A slightly opaque solution is thus obtained, which should be cooled and made up to the proper volume before using.

13. Theoretically we would expect the colors to range from a light yellow to a dark blue, with red tubes holding an intermediate position in the series. This color sequence does often occur, but its occurrence is far from universal. Many

The amylolytic value, Df, of a given stool, may be expressed in terms of 1 c.c. of the sediment obtained by centrifugation as above described. For example, if it is found that 0.31 c.c. of the phosphate-chlorid extract of the stool acting at 38 C. for twenty-four hours completely transformed the starch in 5 c.c. of a 1 per cent. starch solution, then we would have the following proportion:

$$0.31 : 5 \text{ (c.c. starch)} :: 1 \text{ (c.c. extract)} : X$$

The value of X in this case is 16.1, which means that 1 c.c. of the fecal extract possesses the power of completely digesting 16.1 c.c. of a 1 per cent. starch solution in twenty-four hours at 38 C.

Inasmuch as stools vary so greatly as to water content, it is essential to an accurate comparison of stools that such comparison be made on the basis of the solid matter. Supposing, for example, that in the above determination we had 6.2 c.c. of sediment. Since the supernatant fluid was removed and made up to 50 c.c. before testing its amylolytic value, it is evident that 1 c.c. of this sediment is equivalent to 9 c.c. of extract. Therefore, in order to derive the amylolytic value of 1 c.c. of sediment, we must multiply the value (16.1) as obtained above for the extract, by 9. This yields 144.9 and enables us to express the activity as follows:

$$\mathrm{Df}\,\frac{38\,c}{24\,h} = 144.9$$

The above method of calculation is that suggested by Wohlgemuth. In case time and facilities permit of the determination of the moisture content of the feces, it is much more accurate and satisfactory to place the amylolytic values of the stools on a "gram of dry matter" basis. This method of recording the values has been followed in this laboratory in connection with the experiments already mentioned. The amylolytic values of the stools are expressed as the number of cubic centimeters of 1 per cent. starch solution which the amylase content of 1 gram of dry feces is capable of digesting.

I wish to thank Prof. E. W. Washburn and Dr. Paul E. Howe for timely suggestions and Mr. L. T. Fairhall for carrying out certain check tests.

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times the first tubes in the series, i. e., those containing the largest quantities of the fecal extract, will exhibit a bluish cast of color which should not be confused with the starch color reaction. When these blue tubes are present, they are generally followed by yellow, red and blue tubes in order, the final blue tube, of course, being the regulation starch reaction. Occasionally greenish colors will be obtained to the left of the red color. It also sometimes happens that it is somewhat difficult to determine in which tube to the right of the red color the starch blue color is first detected, unless the tube be examined carefully before a strong light. In every instance, however, when these blue and green colors are observed, it is noted that tubes possessing the true dextrin red color are always present between these tubes and the tubes possessing the true starch blue color. It is evident, therefore, that these bluish tints in the tubes to the left of the dextrin color cannot be due to the presence of starch. The cause of the blue color reaction in the first tubes of the series has not been ascertained as yet. This point will be investigated.

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CONGENITAL OBLITERATION OF THE BILE-DUCTS *

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Congenital obliteration of the bile-ducts, though long recognized and reported with relative frequency in medical literature, is still, we believe, a sufficiently rare condition to warrant an additional clinical and pathological report. The history and pathological findings of a case will first be given, and subsequently the incidence, symptomatology, gross and microscopical anatomy and pathogenesis will be discussed.

I. REPORT OF CASE

Patient.—J. M., age 6 weeks, male, Hebrew, was admitted on March 24, 1910, to the children's clinic and subsequently to the service of Dr. Finley of the Montreal General Hospital. The complaint was "yellowness of the skin." The following history was obtained from the mother.

Family History.—The father was living and well at 42 years; the mother was living and well at 35. When 18 years of age, during her first year of marriage, she had a miscarriage at the fourth month. One year later a child was born at full term but died three weeks after birth. A third pregnancy did not occur until seven years later, and the fourth and fifth followed in rapid succession. All of the three latter resulted in full-term, healthy children who are at present 10, 8 and 5 years old, respectively. As far as she remembered, none of them was jaundiced at birth or during infancy.

Personal History.—This, the sixth pregnancy was uneventful, the mother being perfectly well during the entire period. The birth occurred at full term and was normal. The child was fat, healthy-looking and not noticeably jaundiced at birth. It was breast-fed for the first seven days when it was weaned on account of a maternal puerperal infection which necessitated the mother being removed to a hospital on Feb. 16, 1910. There a clinical diagnosis of puerperal infection and pelvic cellulitis was made. When last seen by the mother she is certain that the child was healthy and not noticeably jaundiced. During her absence the child was sent by the Baron de Hirsch Institute to the Montreal Foundling Hospital.

Present Illness.—Through the kindness of Dr. J. L. D. Mason of the Baron de Hirsch Institute and Drs. Wylde and Hill of the Foundling Hospital we subsequently learned that on February 23, the day of admission to the latter institution, and when the baby was two weeks of age, a slight but definite jaundice of the skin and light-colored stools were present; further, that on March 2, after a course of calomel, the jaundice became very deep and the stools clay-colored. The child steadily lost in weight, falling from 7.4 pounds to 6.1 pounds

*From the Clinic and Laboratory of the Montreal General Hospital; read before the American Association of Pathologists and Bacteriologists at the Eleventh Annual Meeting, Chicago, Ill., April 14, 15, 1911.

on March 2, the date of its discharge. On March 8 the mother first saw it again and noted the deep jaundiced hue to the skin and scleræ. About March 14, when the baby was five weeks old, the mother first noticed that the urine was very dark in color, and that it stained the diapers and everything with which it came in contact a deep yellow. The bowels became loose with from four to five colorless and offensive stools in the twenty-four hours. At the same time vomiting developed. From March 2 to the date of admission to the hospital, the child had been fed on cow's milk diluted with equal parts of water. It was brought to the children's clinic on March 24 when a diagnosis of icterus neonatorum, due probably to syphilitic hepatitis, was made. It was sent into the hospital in the service of Dr. Finley, to whose courtesy we are indebted for subsequent observation and study of the case.

Physical Examination.—The patient was a very poorly nourished, male Hebrew child six weeks of age. The weight on admission was 7 pounds, 6 ounces (3,300 grams). The expression was anxious and the child was fretful to a degree. There were no snuffles or other luetic stigmata. The skin was deeply jaundiced and of a distinct coppery hue that offended the eye. Scattered over the skin of the thorax was a fine miliary rash. The scleræ were deeply jaundiced. The muscles were small, the bones normal. The anterior fontanelle was still widely patent. The lymph-glands were nowhere palpable.

Respiratory System: There was frequent cough but no dyspnea. The thorax was small and of the normal infantile type. No beading of the ribs was found. The percussion note was resonant throughout. The breath sounds were puerile, but the presence of adventitious sounds was impossible to determine owing to the constant crying of the child on examination. The heart was not enlarged and the sounds were clear. The pulse was rapid, small, regular and of normal tension.

The abdomen was full and rounded. The superficial veins were everywhere prominent, especially while the child cried, and there was a slight but definite anastomosis visible between the lower thoracic and superficial epigastric veins on either side.

The liver was considerably enlarged but the surface appeared smooth and the edge thin and firm. The upper border of the relative hepatic dulness began at the fourth rib in the right parasternal line, the fifth rib in the mid-axillary line, and extended below the costal border 5 cm. and 3.5 cm. respectively, making a total vertical dulness of 9.5 cm.

The edge of the spleen could just be felt at the costal border.

The urine was deeply bilious, almost porter-colored, and gave the well-marked characteristic rings with fuming nitric acid. The stools were very offensive, perfectly colorless and in this and in their peculiar consistency, resembled white lead.

Course of Disease.—On March 26, 1910, a blood count revealed hemoglobin 50 per cent (Sahli); red cells 3,910,000; white cells 15,800. The smears stained by Wright's method showed normal red cells with a preponderance of polymorphonuclear neutrophils and no pathological cells. A Wassermann reaction on this date was reported absent by Dr. R. P. Campbell. Nevertheless, the therapeutic test of a course of mercurial inunctions was given without benefit.

For the first ten days the temperature ranged between 98 and 99.4; the pulse between 112 and 136; and the respiration 48 to 60 per minute. From April 1 to the day of the child's death, on April 18, the temperature curve was most irregular, ranging between 97 and 101. The pulse grew more frequent, namely, 120 to 138 per minute, while the respiration fell to 40 or less per minute. The child cried constantly day and night but took its nourishment, consisting of modified milk, fairly well.

On April 9 it was noted that even with careful regulation of the diet, the child was steadily failing. The lungs were apparently clear, though there was a frequent hacking cough present. The jaundice persisted and did not vary

noticeably in intensity in spite of frequent doses of calomel. The diarrhea abated; the weight fell steadily to 6 pounds, 9 ounces (2,986 grams) on April 14.

On the afternoon of April 18, death occurred suddenly, after the child had been under observation for twenty-six days and during the tenth week of life.

GROSS AND MICROSCOPICAL ANATOMY

An autopsy was performed by Drs. Wolbach and Baird on April 22, 1910, four days after death, owing to the difficulty of communicating with the mother. The body, which was 51 cm. in length, was very poorly developed and poorly nourished, with marked general jaundice and lividity of the dependent parts. Except for the disappearance of rigor mortis there was otherwise no evidence of post-mortem decomposition.

The right pleural cavity showed fresh adhesions between the diaphragm and the right lower lobe, on separating which a thick, gelatinous, greenish-yellow, fibrinous material was found, small in amount. The left cavity was quite free.

The lungs were both voluminous and air-containing, except the lower right lobe, which presented over its base and posterior surface a nodular appearance, due to small, yellow, rounded, soft elevations 4 to 6 mm. in diameter. On section of this lobe, its anterior half was found riddled with a series of cavities, small, rounded and separated only by thin, smooth walls and containing a thick, gelatinous, greenish-yellow puriform material. A careful dissection of the bronchi showed these cavities to be dilatations of their walls.

The pericardium was smooth and glistening. The heart weighed 20 gm. and appeared slightly enlarged. The endocardium and valves were normal. The myocardium was smooth, firm and of good color.

The peritoneal cavity was smooth and glistening and both parietal and visceral surfaces were stained a deep yellow. The mesenteric lymph-nodes were slightly enlarged, dark and soft, and yellow in color on section.

The liver was enlarged, its lower border reaching 3 cm. below the costal margin. After preservation in Kaiserling, it weighed 370 grams and measured 12.5 cm. transversely, 8.5 cm. anteroposteriorly, and 5 cm. vertically. The weight and measurements were no doubt somewhat greater before preservation but unfortunately were not recorded. The surface was smooth except for an occasional slight depression. The color was a very dark brownish-green. The shape, relative size of the lobes and the position of the fissures were normal. The anterior edge was sharp, the consistency firmer and slightly tougher than normal. On section the cut surfaces were smooth, dark and mottled, due to minute greenish-black areas separated by a delicate dark red tracery.

The gall-bladder was very small and presented as a bulbous enlargement of the cystic duct 1 cm. long and 0.05 cm. broad. It could be filled with water from a hypodermic syringe, but no fluid escaped from the cystic duct. The anatomical relations of the gall-bladder, hepatic, cystic and common ducts and the vessels of the liver were normal. The hepatic, cystic and common ducts consisted of fibrous cords in which no lumen could be found either by a probe or by injection with a hypodermic syringe.

On opening the duodenum, the papilla of Vater was easily found. No fluid could be forced through it by milking the bile passages. A probe passed into the papilla entered without resistance into the pancreatic duct. A very careful dissection with a probe in the pancreatic duct failed to show any other structure entering the duodenum in the neighborhood of the papilla. A similarly cautious dissection downward along the cord representing the common duct carried one into the head of the pancreas, where the common duct lost itself in the substance of the pancreas as a number of delicate fibrous strands (Fig. 5).

The spleen weighed 25 gm. (15 gm. is the average weight of the spleen in the third month), was smooth, dark red in color and of normal consistency. On section the surface was dark red and yielded no pulp on scraping.

The pancreas was normal in appearance and consistency. A careful dissection, as stated above, showed that its duct opened normally into the duodenum. The gastro-intestinal tract was normal throughout.

The kidneys weighed 45 gm.; both were smooth, dark red in color and of normal contour. The capsules peeled off easily. On section the cortices and pyramids were normal. The adrenal glands and genital organs were normal. The bone marrow appeared normal.

The brain weighed 440 gm. and presented no apparent lesion. The anatomical diagnosis was: congenital obliteration of the bile-passages; rudimentary gall-bladder; bronchiectasis (local); fibrinopurulent pleurisy and icterus.

Microscopical Examination.—Sections were stained with Scharlach red, Mallory's connective tissue, phosphotungstic acid hematein and the eosin-hematoxylin methods.

The heart was quite negative.

A section from the normal-appearing portion of the lung showed moderate injection of the alveolar capillaries. The vessels and bronchi were negative. Occasional groups of alveoli contained a few polymorphonuclear leukocytes and desquamated epithelium. Sections from the right lower lobe were riddled with cavities, mostly circular in outline, and containing puriform material and separated from one another by narrow zones of flattened alveoli filled with exudate. In many of these cavities portions of the periphery were bounded by columnar epithelium. Some of the small cavities were completely surrounded by cuboidal cells, a few of which showed ciliated borders. In most instances the border of these cavities was sharply demarcated and occasionally showed a definite line suggesting the basement membrane of the bronchus. By the use of Mallory's connective-tissue stain, smooth muscle fibers were occasionally found external to the line bounding the cavity, which was further evidence that these cavities were bronchiectatic in origin. The contents of the cavities were composed chiefly of polymorphonuclear leukocytes and cell detritus. There were numerous phagocytic cells containing nuclear remains and, rarely, red-blood corpuscles. Where the boundaries were poorly defined and the adjacent alveoli merged in the puriform area, there were occasional compact masses of eosin-stained material filled with migrating leukocytes and nuclear fragments, remotely suggestive of caseous material. Stains for tubercle bacilli, however, yielded negative results. The alveoli between the puriform areas were compressed and many contained pus, a few fibrin and a few large, sponge-like, mononuclear cells. All of the bronchi in these sections were filled with puriform material. The blood-vessels were negative. The interlobular connective tissues were edematous.

The liver was moderately injected. The normal area of the liver columns was preserved, but there was a distinct loss of cells and increase in the connective tissue about the hepatic veins and a fairly marked increase about the portal spaces. The liver-cells themselves stained normally. At the centers of the anatomical lobules, the bile capillaries were filled with dark brown inspissated bile and were often greatly distended or ruptured. There were masses of bile lying outside the liver columns, some of which were taken up by endothelial cells. In most lobules there was a considerable increase of connective tissue in the spaces formerly occupied by liver-cells and now containing pigment and phagocytic cells. The cells of the intermediate zone were normal, except for a small amount of pale, brown, granular pigment scattered throughout the cytoplasm. At the periphery of the lobules there was often an irregular increase of the connective tissue extending inward from the portal space between the liver columns and sinusoids. Many of the portal spaces contained a large number of tortuous bile-ducts, empty of bile. The bile capillaries at the periphery of the lobules were easily demonstrable, but were also empty. Most of the large bile-ducts in the portal spaces showed no evidence of dilatation and contained a circular reticulum only; rarely a dilated bile-duct was found filled with inspissated bile and lined with flattened epithelium. No fat could be demonstrated.

The spleen showed moderate injection. The Malpighian bodies were normal. The pulp contained a few large mononuclear cells, phagocytic for red-blood corpuscles.

The kidneys were markedly injected. The glomeruli were of the normal fetal type. The epithelium of the convoluted tubules was swollen and granular. There was an occasional hyalin cast in the collecting tubules. The adrenals and other organs were normal.

The histological diagnosis was: bronchiectasis of the lower lobe of the right lung; hepatic cirrhosis of a mixed type; subacute nephritis.

II. ETIOLOGY AND SYMPTOMATOLOGY

Historical Note.—For many years icterus neonatorum was recognized before it was realized that a certain small percentage of these cases was associated with malformations of the biliary tract. From time to time isolated examples have been reported of icterus developing at birth or shortly afterward, which was found post mortem to be associated with stenosis or even complete obliteration of the hepatic, cystic or common ducts. John Thomson,[1] in 1892, was the first writer to assemble the various cases in the literature. He was able to collect forty-nine protocols and wrote a classical article which has formed the basis for most of the subsequent reviews. In 1901, H. D. Rolleston and L. B. Hayne[2] added nine cases to Thomson's series, bringing the total to fifty-nine. The last important article was published in 1908 by Lavenson,[3] who abstracted sixty-two acceptable cases and added a case of his own.

We have succeeded in finding thirteen additional cases, which either have been overlooked by Lavenson (e. g., Kirmisson and Hebert,[4] Cattaneo,[5] Demel,[6] Bushnell,[7] Emanuel,[8] Simmonds,[9] [two cases], Miller[10]) or have appeared since his paper (Parkes Weber,[11] Peck,[12] Petit and Merle,[13] M. and R. C. Ferrard[14]).

This now brings the total number of cases of congenital obliteration of the bile-ducts to seventy-six, inclusive of ours and exclusive of those directly associated with syphilis (Rolleston,[15] Simonini[16]).

Predisposing Factors.—1. Health of Parents: Some minor rôle may be played by the health of the parents prior or subsequent to conception. Thomson found that of ninety-six parents, five had had at one time or another, syphilis. In others, again, there was a history of recent severe digestive derangement (e. g., Ferrard[14]). In our case, while no definite history of lues could be elicited, it is noteworthy that during the early married life of the mother, there was a miscarriage at the fourth month, that the second child, though born at full term, died three weeks after birth, and that the third pregnancy did not occur until seven years later.

2. Condition of Other Children in the Family: Several authors have noted a tendency for more than one child of the same parents to have icterus, two authors reporting two cases in the same family in association with a defect of the bile-passages. Again, another author reported twins, both of whom were jaundiced but one recovered so that the condition of its bile-passages was not ascertained.

3. The Character of Labor: This has been for the most part entirely normal; at least no history of excessive trauma has been noted in any of the series. With Thomson, we admit that trauma or exposure at the time of birth might cause a local peritonitis and so, obliteration of the ducts.

4. Premature Birth: This plays no rôle, for, though it was found five times in Thomson's series, in all of the five jaundice did not develop until some time subsequently.

5. Sex: Curiously enough, male infants seem more predisposed than female, but in so small a series too much emphasis should not be laid on this factor.

6. Congenital Syphilis: Six, possibly nine of Thomson's series presented evidence of congenital lues at birth or shortly afterward. In our case there were no apparent stigmata and the Wassermann reaction proved negative. Hence, it is safe to say that in the majority of cases there is no sign or suspicion of lues.

7. Erysipelas: This, which has been suggested by one or two writers as a possible predisposing factor, can be dismissed without further comment.

Symptomatology.—1. Onset of Jaundice: The period of the onset of jaundice varies considerably. In some cases the icterus is noticed on the day of birth, in others not until the child is 2 weeks or more old. Naturally, there are many possible sources of error for such discrepancies as, for example, the jaundice may be very faint at birth and will only be noted when it becomes of a certain intensity. With Rolleston we cannot accept Treves' remarkable case in which the onset of the jaundice did not occur until the third year of life and in which a successful operation for the relief of the obstruction was performed at the age of 17. As Rolleston suggests, the obstruction was in all probability due to calculus or some postnatal infection of the duct. At least one must admit that some event at birth plays a part in determining the onset of the color. Legg and Murchison believe that twelve to forty-eight hours must elapse before obstruction of the bile-ducts and the appearance of the jaundice occur. "The enormous change which the circulation of the liver undergoes about the time of birth constitutes the most probable explanation of the relation between the onset of jaundice and that event." So even if one accepts a congenital malformation as the cause for the obliteration of the ducts, one can explain the lapse of time between the birth and the period of onset of the jaundice by the fact that the cells of the child's liver which had long ceased to secrete bile owing to the permanent blocking of the ducts, are stimulated by the sudden change in the circulation to return to their natural function of bile production.

2. Character and Progress of the Jaundice: The icterus is always progressive and sooner or later becomes marked, being of a deep greenish

hue — in our case of that peculiar coppery tint that is actually offensive to the eye. Sometimes the degree of jaundice appears to vary from day to day and in some cases it becomes paler before death. It is a curious fact, however, that even when one duct is pervious, the jaundice may be as deep as in a case with complete occlusion.

3. Urine: The urine is always said to contain large quantities of bile pigments except in one case reported where none was found present.

4. Meconium: In some cases it was colored and in others quite white, due, no doubt, to the fact that the occlusion of the ducts occurred at different periods of intra-uterine life. In no case was a dark meconium followed by normal-colored feces, even if the icterus did not develop until much later. Hence one may conclude that the biliary obstruction is always considerably advanced at birth. Further, from this it would appear that the obliteration of the ducts is not due to an arrested development, though there may be a very early obstruction to the lumen of the biliary passages.

5. Stools: The color of the stools will vary with the degree of obstruction; thus, where the obstruction is not complete the stools may be green or brown. Where, however, the obstruction is extensive, the color varies from white to cream and in one of the reported cases and in ours, resembled white lead. In certain of the cases in which there was found post mortem complete obstruction, the stools were noted to have a greenish tinge. The possible explanation of this green color is first, a mixture of the stool with bile-stained mucus; second, the result of the administration of mercury which notoriously produces green-colored stools; and third, the influence of microorganisms.

6. Vomiting: This seems of rare occurrence and was noted in but a small percentage of the cases in the literature — 18 per cent. in Thomson's series. It was rather a prominent feature in our case, especially in the terminal stages.

7. Hemorrhages: The occurrence of hemorrhages into the skin and conjunctivæ or from the mucous membrane of the nose, gastro-intestinal tract, and from the umbilical cord, has been noted in nearly 50 per cent. of the cases. It was absent in ours. This hemorrhagic tendency is similar to that present in all cases of obstructive jaundice in the adult and is always a serious omen but not necessarily fatal in its results. The cause of it is obscure but several possible explanations have been advanced: First, an impoverishment of the blood, that is, a diminution in the ratio of red blood-cells to the fibrin content; second, hemolysis of the red cells by the biliary acids circulating in the blood; third, parenchymatous degeneration of the blood-vessels similar to the change that occurs in the glands and muscles as a result of the bile acids; and fourth, the presence in the blood of ptomains formed in the process of digestion which the diseased

liver is unable to render innocuous. Thomson discards the first three possibilities and accepts the fourth as the most plausible.

8. Emaciation: Contrary to what one might expect, this is not an early symptom, which, as Thomson suggests, shows that the presence of bile is not very necessary for ordinary digestion. If, however, the child lives long enough, emaciation will develop, due to the secondary hepatic changes and consequent interference with the proper assimilation of fat, and other important functions.

9. Duration of Life: If one excludes the patient who died from umbilical hemorrhage — a not uncommon accident in these cases — the majority lived more than one month after birth. One only was still-born; eleven lived less than a week; eight lived one to four weeks; and fourteen lived from one to four months and sixteen more than four months after birth. Our patient, who lived ten weeks, is, therefore, not remarkable in the duration of life in spite of the extensive obliteration of the biliary tracts. Lavenson found in his series of sixty-two cases that only three patients lived longer than eight months — two until the ninth and one until the eleventh month.

III. GROSS AND MICROSCOPICAL ANATOMY

Ascites was pronounced in two of Thomson's series while peritoneal adhesions were found in five others. The liver was generally but not always increased in size. One case of an atrophic liver was noted. The color was usually dark green and often of a peculiar morocco-leather appearance, owing to the dark green color and the finely granular surface. The consistency was tough, suggesting the presence of an increased amount of fibrous tissue. The portal vein and vessels were normal except in four cases which were probably luetic in origin, and in which there was obliteration of the portal vein.

The condition of the bile-passages and gall-bladder can best be described under four groups. In the first group there was no passage from the liver to the duodenum, though the gall-bladder and cystic duct were patent. In the second group a passage was present from the liver to the duodenum but no cystic duct or anything to represent the gall-bladder. In the third group both cystic and hepatic ducts were obliterated. Our case would be included in this division which is, by far, the commonest. In the fourth group there was obliteration at a variable point below the juncture of the cystic and hepatic ducts.

There is a great variety in the secondary changes in the external excretory apparatus and there appears to be no relationship between the presence of jaundice at birth and the nature of the malformation. Thus, the most severe malformations occurred in cases which lived for several months. A dilatation of the canal above the point of obliteration was not

invariably present but may exist to an enormous extent (e. g., Miller's case[10]). The obliterated duct may remain as a fibrous cord or entirely disappear. If the gall-bladder exists, its contents vary from a peculiar thick, syrupy bile to a clear watery fluid. The latter is true if the child has lived more than a month.

In Thomson's series the spleen was usually found enlarged, as was observed in ten of twelve cases in which its condition was noted. Sometimes it was very large.

Fig. 1.—Low-power view showing intralobular and perilobular connective tissue increase. The small black areas in one portal space are inspissated bile in bile-ducts.

Histological Anatomy.—A microscopical examination was made in but nine of the earlier cases, in all of which, however, a hepatic cirrhosis was present, while masses of inspissated bile were noted in the ducts and liver-cells. In the more recent cases a more or less complete histological study has been made. The chief point of interest is that at autopsy at least, the liver shows a more or less advanced cirrhosis of the mixed type with the biliary cirrhotic features predominating. The detailed picture is well illustrated by our protocol.

IV. PATHOGENESIS

This is one of the moot questions in the literature of this subject. Thomson, Rolleston and Lavenson, as representatives of the most distinct views, will be most freely quoted by us. As pointed out by Lavenson, one can divide the theories advanced into two classes: (I) that which considers the disease as a primary involvement of the ducts; (II) that which considers it as a primary involvement of the liver, i. e., a cirrhosis.

I. The Theory of a Primary Involvement of the Ducts.—In support of the view that the obstruction of the duct is the primary condition and the cirrhosis the result of the ensuing biliary stasis, Lavenson advances the following facts:

Fig. 2.—High-power view, showing proliferation of bile-ducts in a portal space.

First, in both adults and children biliary stasis results in the same chain of events and the same pathological findings as are present in the cases under discussion.

Secondly, Steinhaus, Pick, Lannaeq, Gerhardt, Beloussow, Harley and Tsunoda[23] have shown experimentally in animals the same changes in the liver as are found in cases of biliary stasis in man.

Under this head the possibilities to be considered are: (1) an anomaly of development; (2) organization of a non-specific inflammation either within or without the ducts; (3) syphilis.

1. The Theory of Congenital Malformation.—This theory originally was supported by Thomson,[1] who believed in a primary congenital malformation of the duct which resulted in narrowing of the lumen and predisposed to a catarrh, and so to a blocking and finally caused the complete obstruction of the duct. This, in turn, led to a biliary cirrhosis of the liver. He believed that the obliteration was usually complete at an early period of intra-uterine life. He pointed out that the appearance of jaundice in several members of a family supported this congenital developmental theory and explained the fact that when the onset of jaundice was not contemporaneous with the blocking of the duct (i. e., did not occur

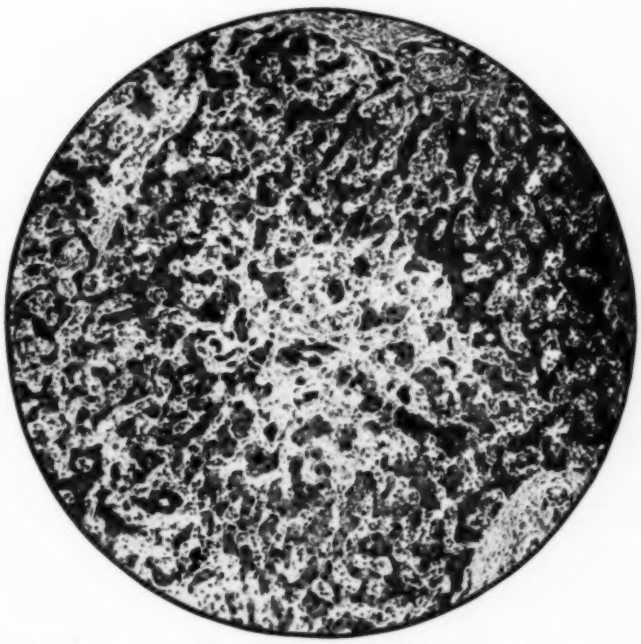

Fig. 3.—Medium-power view of one anatomical lobule, showing central increase of connective tissue and distended bile capillaries.

until several days after birth) it was due to circulatory changes that occurred in the liver at birth.

Weber believes that some cases of congenital obliteration of the bile-ducts are due to a primary developmental malformation similar to that in congenital valvular disease of the heart. But in another paragraph[11] he writes: "These congenital changes were doubtless partly inflammatory in origin and as usual were unaccompanied by congenital defects elsewhere in the body."

Bushnell[7] and Simmonds[8] support this view of an error of development. Fuss and Boye also "believe that the absence of any cystic enlargement of the gall-passages and the enormous hypertrophy of the liver-tissue speak rather for a developmental error. The liver changes may be secondary to bile stagnation, analogous to the experimental cirrhosis from constriction of the common duct." But they also admit "another possibility is a primary liver disease which descending produced an obliteration of the ducts."

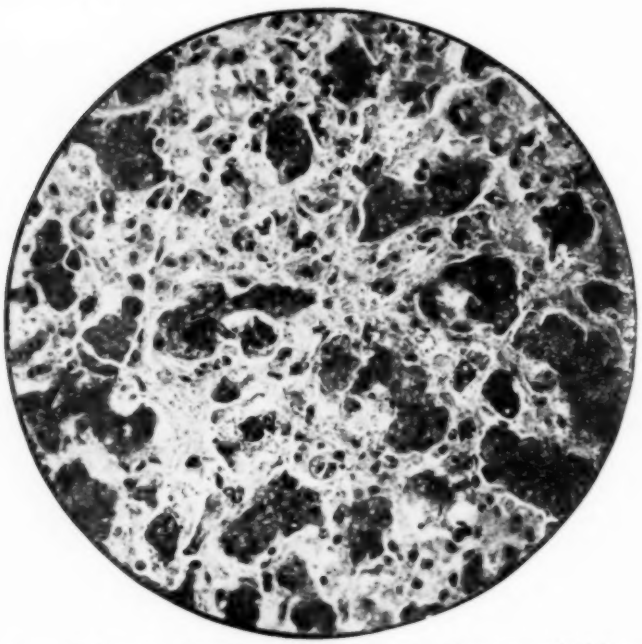

Fig. 4.—High-power view of center of Figure 3. Shows atrophied liver-cells and inspissated bile in the connective tissue. Rupture of the bile capillaries and atrophy of the liver-cells are the probable factors leading to the liberation of the inspissated bile.

Thomson's original theory was carried still further by Lavenson,[3] who believes that the atresia is primary and that the cirrhosis results from the biliary stasis. He states that the fibers of Renak (the offshoots from the embryonic solid cord that buds out of the primitive gut to form the liver and hepatic ducts) remain solid instead of developing a lumen as they do normally. Another possible explanation is a faulty union of the two rudimentary portions of the ductus hepaticus and ductus choledochus. This receives support in a certain proportion of the cases in which the obliteration is found at the point of union of these two portions.

Furthermore, the occurrence of other undoubted anomalies of the liver and its appendages (e. g., entire absence of the gall-bladder, cystic duct, caudate and Spigelian lobes, transposition of the portal vein and artery[4]) and occasionally congenital defects in other portions of the body (e. g., situs inversus,[17] cystic liver and kidneys, patent ductus Botalli,[5] and even absence of right hand and ulna) "lead one to believe that a large percentage of the cases are a result of a congenital defect of development." Further, Lavenson considers that "the term 'atresia of the bile-duct' better expresses the existing condition than 'obliteration of the bile-ducts.'"

Though, as we shall see in the next paragraph, Thomson repudiated for a time the theory of congenital malformation, in his last article[26] he has adopted again his original doctrine and wrote: "I am inclined to return to the view I formerly held as to a relative narrowing of the bile-ducts of developmental origin being probably the primary cause of all the other changes."

2. Organization of a Non-Specific Inflammation of the Ducts.—In his second article,[18] Thomson admitted if the obliteration were due to an arrest of development, the former would occur at the same site in the majority of cases. This is not the case. The same would be true if it were due to a local stimulus within the tube like a calculus, for example, as was found in two instances.[26] He therefore advanced another suggestion, namely, that irritative substances which were present in the bile set up a descending cholangitis which resulted in interference with the passage of the bile and finally in biliary cirrhosis just as occurs in animals in which the common duct is tied.

We quite agree with Lavenson when he states that the preexistence of a non-specific inflammation is impossible to either deny or affirm, for when the case comes to autopsy the acute process is replaced by fibroid changes not characteristic of any form of inflammation. Nevertheless, the relative infrequency of a true catarrhal jaundice in infants is against this theory.

Obliteration of the ducts from without by adhesions resulting from a fetal peritonitis may be the cause of a certain number of these cases according to both Thomson[1] and Rolleston.[14] The former found in five of his series, peritoneal adhesions present in the neighborhood of the ducts implicating the blood-vessels, and believed that peritonitis is a common occurrence in fetal life, though he frankly admits it is most often due to syphilis. It seems more probable, however, that the peritonitis is a result and not the cause of the obliteration of the duct.

3. Syphilis.—Petit and Merle[13] regard the process not as an arrest of development but as an inflammatory degenerative process of the biliary tract in intra-uterine life, probably syphilitic in origin in spite of the

absence of a history of lues. They term this condition fetal angiocholitis. M. and R. C. Ferrard[14] also support this view and make use of the same term.

While one must admit that congenital luetic hepatitis and choledochitis may simulate the disease under discussion (e. g., Beck, Rolleston[15] and Simonini[16]) the absence in the latter of the numerous definite stigmata of syphilis and the Wassermann reaction make this theory untenable.

II. The Theory of a Primary Congenital Cirrhosis.—Rolleston put forward this hypothesis and advanced in support the following facts:

A. The almost constant occurrence of cirrhosis in these cases in infancy as compared with the rarity of cirrhosis of the liver following obstruction of the bile-ducts in later adult life.

B. The large size of the liver which resembles the liver of biliary hypertrophic cirrhosis. In adults, on the other hand, simple obstruction of the bile-passages causes at first an enlargement of the liver and subsequently atrophy.

C. The large size of the spleen in the infant, a phenomenon not encountered in the uncomplicated biliary obstruction of the adult.

D. "The fact that in some instances several cases of this rare disease have occurred in the same family."

To explain the occurrence of the biliary cirrhosis in the new-born child, he writes that "poisons pass by the blood from the placenta to the fetus by the umbilical vein. Some of this toxic blood produces ordinary portal or multilobular cirrhosis. Some of the blood, however, passes directly into the general circulation by means of the ductus venosus, hence by the hepatic artery to the liver where it will set up in the small intrahepatic bile-ducts a cholangitis and monolobular cirrhosis resembling that seen in hypertrophic biliary cirrhosis." In this way both a portal and biliary or what is termed a mixed cirrhosis is produced. This cholangitis descends to the larger ducts. Now, as the bile-ducts are extremely small at birth, any inflammatory changes will, on account of the small size of the lumen, produce a stenosis much more readily than in later adult life. He not inaptly compares this descending obliterative inflammation of the larger extrahepatic ducts with the processes at work in an obliterative appendicitis.

Rolleston frankly admits that against this theory is the unanswerable fact that the poisons which cause the condition in the liver of the child must circulate in the mother, and that she should show evidences of its influence. He further remarks that it is possible that there are several conditions at present included under the title "congenital obliteration of the ducts," and that some cases are due to constriction of the duct by a localized peritonitis and deserve the title of "congenital obliteration of

the ducts" better than those cases which are intimately associated with cirrhosis. Emanuel,[8] among others, supports this theory because of the fact that there was a fibrosis of the pancreas in his case without much secondary involvement of the pancreatic ducts; in other words, there was a toxic fibrosis of the liver, spleen and pancreas.

Lavenson strongly attacks Rolleston's views and meets each argument by a counter one.

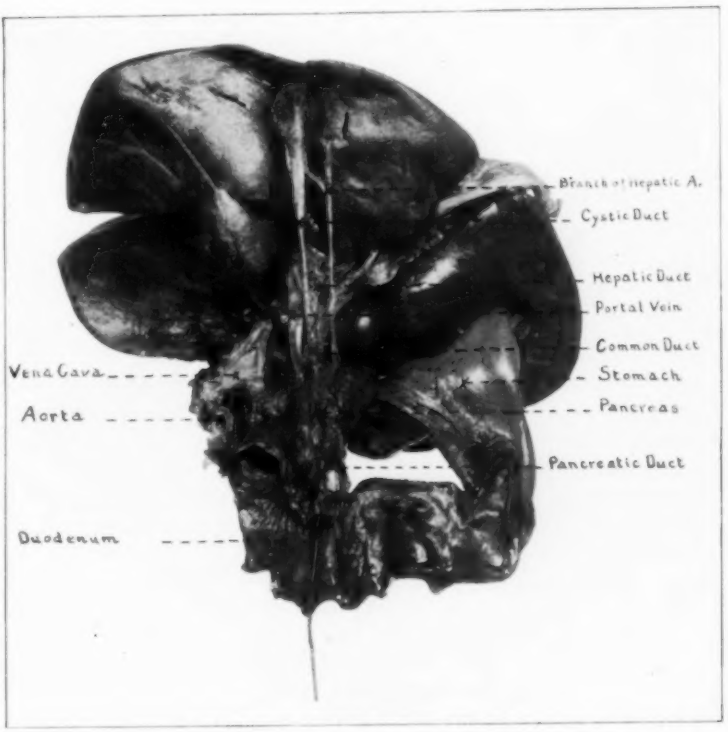

Fig. 5.—Obliteration of the bile-ducts.

A. Thus he points out that the statement that cirrhosis following biliary obstruction in the adult is rare, cannot be accepted in view of the fact that Mangelsdorf[22] and Ford were able to collect reports of some 208 cases and that no doubt many cases occur and are not recorded. Further, Lavenson asks why, if Rolleston's contention be true, is not biliary obstruction more common in Hanot's cirrhosis of adults? Another important point is that Lavenson found that in twenty-four of sixty-two cases the obstruction was in the duodenal portion of the bile-duct while

the hepatic portion was patulous. Lastly, some patients who died shortly after birth showed only the earliest stages of cirrhosis because the biliary stasis had not existed long enough.

B. Lavenson admits that in the condition under discussion, the liver is large just as it is in Hanot's biliary cirrhosis, but it is also true of cirrhotic livers following biliary obstruction in adults, and quotes the following: "The livers in these cases of obstructive cirrhosis are greatly enlarged, with a rough jaundiced surface and considerable perihepatitis."[22]

C. To controvert this point he cites from Rolleston's text-book in the section on cirrhosis from biliary obstruction in adults: "The spleen is sometimes small or of normal size but in cases where considerable fibrosis of the liver coexists with obstruction of the larger ducts, there may be a considerable enlargement (of the spleen), though not to the same degree as in hypertrophic biliary cirrhosis."

D. Lavenson would accept only Binz's cases as examples of the disease occurring in the same family. He rejects the other cases on the grounds of insufficient data: (West's two cases, Thomas, Arkwright, Bloomfield[25] and Pearson). Lavenson concludes with the remark: "There is little or no support of the view that the obstruction is secondary to the cirrhosis."

The writers agree with Rolleston,[2] Griffith[21] and Peck[12] that there is probably some truth in all the theories advanced; some cases may be due to an anomaly of development, others to a simple inflammation of the ducts, and still others to a primary congenital cirrhosis. No one theory will suffice for all the cases reported under the title of "congenital obliteration of the bile-ducts."

V. DIAGNOSIS

1. Simple Icterus Neonatorum.—This condition is of relatively frequent occurrence and was present, according to Holt, in 300 of 900 consecutive births at the Sloane Maternity Hospital. The intensity of the jaundice is usually slight and it rarely persists even in the most severe cases for more than two weeks. Furthermore, the color of the stools remains unaltered and, as a rule, the skin of the child even in the absence of treatment, soon returns to a normal color.

2. Congenital Syphilitic Hepatitis.—In this condition, apart from the presence of other luetic stigmata in the child or the history in one or the other parent of a venereal infection, there may be a great enlargement of the liver and occasionally ascites, but jaundice is rare and then usually very slight in character. Post mortem, there is found a great liability to an obliteration of the portal vein.

3. Septic Jaundice.—This may exist in association with phlebitis of the umbilical vein. This is a severe and very fatal form in which hemorrhages from the cord are the prominent feature.

4. The Ictérie Splénomégalique of the French.—This rare disease occurs in older children and is associated with a gigantic spleen, ascites, marked enlargement of the abdominal veins, deep jaundice, clubbing of the fingers, and stunting of the general growth.

VI. TREATMENT

Medicinal treatment is certainly valueless. Calomel, gray powder and saline purgatives have been tried by all but, naturally, without success. Surgical procedures cannot offer much hope except in those cases in which the obstruction is incomplete and confined to the lower or duodenal end of the ducts. In such cases a union between the patulous portion of the duct and some loop of the intestine might be procured. Giese, J. L. Morse and Murphy,[20] and Putnam have reported cases in which operative measures were tried but without success.

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DUODENAL DIAGNOSIS: X-RAY CONSIDERATIONS

A TECHNIC FOR FLUOROSCOPY *

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The estimation of gastro-intestinal pathology is being placed on a safer basis than subjective symptomatology. The stomach may be the barometer of digestive function but not so frequently the site of the pathologic conditions. Mayo[1] says that "the stomach has been credited with a host of diseases which it never possessed and has received an amount of treatment for suppositious conditions that is little credit to the medical profession. These mistakes have been due mainly to fundamental misconceptions of the function of the stomach, its relation to diseases in general and especially to those of the digestive tract. Mistakes in diagnosis are more often the result of lack of examination than a lack of knowledge. Prolonged laboratory examination and investigation has been productive of much harm. A scientific but deadly delay."

The primary etiological factor in duodenal ulcer is as obscure as that of gastric ulcer. Predisposing conditions and contributory causes depend on interference with normal function in the duodenum and are of wide latitude. Mechanical and chemical causes are dependent on the motility of the stomach and duodenum and on alterations in the pyloroduodenal anatomy. Most duodenal ulcers are found at that point which receives the impact of the acid chyme as it is ejected from the pylorus. The duodenal preference is an alkaline reaction, and the forcible mechanical contact of chemically disagreeable ejecta could do much to break down a normal or weakened resistance. The control of the pylorus is extremely delicate at the best. The rate of the pyloric outflow is governed by the rapidity with which the ejected acid chyme is neutralized by the alkalinity of the duodenal secretions. The presence of acid in the pyloric antrum promotes the opening of the pylorus, but the presence of this acid content in the duodenum immediately causes the pylorus to close. The pyloric function is more under the control of the duodenum than the stomach (Mayo).

The greater frequency of duodenal ulcer in men may be dependent on the fact that the first or ascending portion of the duodenum is higher in

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1. Mayo, W. J.: Diseases of the Stomach and Duodenum from a Surgical Standpoint, St. Paul Med. Jour., 1911, xiii, 1; Ulcer of the Duodenum, Jour. Am. Med. Assn., 1908, li, 556.

men than in women, so that the alkaline secretions do not reach or rise as high to neutralize the acid chyme with physiological rapidity. Duodenal ulcers usually occur above the bile-ducts, are single and on the upper circumference, and are more likely to involve the pylorus and stomach than to progress in the opposite direction.

The first or superior portion of the duodenum may be regarded as a physiological part of the stomach. The similarity in the symptoms of gastric and duodenal ulcers also warrants this view. Both Schwarz[2] and Holzknecht,[3] by the use of the fluoroscope and bismuth suspensions, noted that the food when ejected from the stomach remained for some little time in the superior or first part of the duodenal segment before advancing, at a comparatively rapid rate, through the remaining duodenal canal. Holzknecht calls this first duodenal segment the *Püfferraum* or teasing-room. By the fluoroscope he finds that this portion has no peristalsis normally. It acts like a storage-room for the chyme as it is ejected from the pylorus by the peristalsis of the antrum. It can hold quite an amount of chyme and does not rapidly pass this on unless its capacity is taxed, when it permits the surplus to be passed on in small coin-sized masses. These masses normally are not sharply defined by the fluoroscope but they may be distinguished as small masses, not nearly as large as the lumen of the duodenum, and they follow one another every few seconds, resting momentarily at intervals.

Considering that the first part of the duodenum has practically the same functions as the cardiac portion of the stomach, that of a reservoir, we may apply the principles of gastric fluoroscopy to duodenal diagnosis. It is easier to obtain fluoroscopic information regarding the late pathological changes produced by duodenal ulcerations, such as strictures and stenoses, dilatations, diverticula and hour-glass duodenums. In these late manifestations of pathology the bismuth suspensions cast characteristic shadows; the strictures and stenoses prevent the rapid or normal progress of the bismuth, and it dams up according to the degree of the stenosis or dilatation. If the dilatation is not dependent on a stenosis but merely is due to a lack of tonicity in the musculature, we would note a tardy progress of the bismuth through the dilated portions, and the distinct line or contracted area of a stenosis would be absent. In diverticula the pocket might become filled with the bismuth and so demonstrated as an abnormal shadow without the lumen of the duodenum but contiguous thereto. In all these late or chronic diseased conditions, it is not necessary but it is advantageous to employ special means of filling the duodenum with bismuth emulsions or suspensions. Bismuth and water pass rapidly through the pylorus of a fasting patient, and with

2. Schwarz: Berl. klin. Wchnschr., 1908. No. 21; Abstr. in Fortschr. a. d. Geb. d. Röntgenstrahlen, 1908, xii, 435.

3. Holzknecht: Deutsch. Ztschr. f. Chir., 1911, cv, 54.

even a mild degree of pyloric spasticity or physiological closure of the pylorus, the suspension would fill up the duodenum before the duodenal pathology permitted the passing of such suspensions beyond. It is in the acute spasmodic functional disturbances of motility that the artificial filling of the duodenum is necessary.

This artificial filling may be accomplished by using a Gross duodenal tube, which is a small rubber tube tipped with a small ball. For this fluoroscopic examination it is necessary to substitute a lead ball for the aluminum one that Gross first devised, so as to obtain an image by the Roentgen ray. The patient swallows the ball and tube, it passes the pylorus and then the bismuth suspension is poured directly into the duodenum, as there are small holes for the exit of the fluid, just above the small ball.

Barclay[4] has frequently noted by ordinary fluoroscopy that a shadow which is separated from the pylorus persists beyond the pylorus and remains uninfluenced by the stomach peristalsis. There was usually a normal stomach shadow but a violent peristalsis. The pylorus opened more frequently and the gastric contents passed more rapidly, so that the stomach emptied itself in a short time, perhaps in one-half hour. Whenever he found this normal stomach shadow with excessive peristalsis passing the food rapidly, he considered it diagnostic of duodenal ulcer.

Distention changes in the duodenum and small intestines may be due to obstruction of the ileum. The obstruction of the ileum may be due to kinks produced by its mesenteric attachments, or to an anchored appendix, or to the weight of a loaded cecum which lessens the lumen of the ileum as it passes over the pelvic brim. Lane[5] has been unable to satisfy himself regarding the mechanism of this duodenal distention. At first he thought that the ileac obstruction dammed back the intestinal contents but that this could only be a reflex cause, as the jejunum emptied itself rapidly. Later he considered the distention secondary to the compression or obstruction of the third part of the duodenum by the strain exerted by the mesentery of the jejunum. Jordan[6] has always been able to demonstrate this duodenal distention in Lane's cases, by the fluoroscope and bismuth suspensions. The bismuth would advance normally to the third portion of the duodenum but here it halted, and only after four and nine hours was the obstruction seen to relax and eject some bismuth. During the time that the duodenum was filled, active and often violent peristalsis was seen in the walls of the duodenum. The stomach itself emptied normally, although usually it was dilated and elongated.

Lane and Jordan report four cases in which they demonstrated the distention of the duodenum by the fluoroscope and bismuth. They fre-

4. Barclay: Arch. Roentgen Ray, 1910, xv, 174.
5. Lane: Surg., Gynec. and Obst., 1911, xii, 222.
6. Jordan: Surg., Gynec. and Obst., 1911, xii, 226; quoted by Lane.

quently found duodenal ulcer associated in this class of cases. Operative interference disclosed usually a vertical downward pull on the commencement of the jejunum with a torsion which rendered evacuation of the duodenal contents difficult. The cecum was frequently found fixed by adhesions in the iliac fossa and the iliac obstruction was purely static, owing to resistance of the brim of the pelvis.

Holzknecht diagnosed five cases of duodenal stenosis by the fluoroscopic examination. The duodenum filled up behind the stenosis, so that the walls were in sharp contrast. The duration of the filling depends on the depth of the stenosis and the degree of the disproportion between the narrowness of the stenosis and the peristaltic strength of the stomach and duodenum, and on the mass of the ingesta in the duodenum. The duodenum, when filled behind a stenosis, exhibits worm-like convulsive contractions without visible effect on the mass, i. e., there is no outpouring through the stenosis. This peristalsis of the duodenum occurred at rhythmical intervals of about seven seconds and lasted about two or three seconds. Where there was a high degree of stenosis there appeared to be an atony of the dilated duodenal walls, probably owing to lack of compensation in the musculature. The degree of the stenosis was estimated by the length of time during which bismuth contents remained in the duodenum, which varied from a short time in spastic conditions to twenty-four hours in organic stenosis.

Crane[7] recently called attention to the possibility of outlining the head of the pancreas, or estimating its size by plotting the curve of duodenum as the duodenum encircles the head of the pancreas.

AUTHOR'S TECHNIC

The method of introduction of the Gross duodenal tube has been described fully by Gross.[8] Briefly, the small tube with a lead ball at the end is swallowed about fifteen minutes after the patient has taken a glass of milk. The patient takes an easy position recumbent on the right side with the hips elevated. After about one-half to one hour the patient is fluoroscoped to see if the ball has passed the pylorus. A small amount of bismuth and water may be given (not through the tube). If the tube is in the duodenum it will appear independent of this bismuth stomach shadow. When it is determined that the lead ball at the end of the tube has passed the pylorus and is in the duodenum, a suspension of bismuth in water (one-half ounce of bismuth oxychlorid to 6 ounces of water) is funneled into the tube, and thus it reaches the duodenum independent of pyloric activity.

7. Crane: Tr. Am. Roentgen Ray Soc., 1910. Reference from Am. Quart. Röntgenol., 1910, ii, 269.

8. Gross: Duodenal Ulcer, Jour. Am. Med. Assn., 1910, liv, 1365.

The patient, just previous to the injection of the bismuth suspension through the tube, is placed on the simple apparatus illustrated in Figure 1. The patient is brought to a horizontal position on the right side, as in Figure 2, just before the suspension is introduced, so that the duodeno-

Fig. 1.—Apparatus for use in fluoroscopy.

jejunal junction will be at the highest point and the duodenum will have the position of an upright U. We are accustomed to use this simple apparatus with a Beclere fluoroscopic stand.

This method of filling the duodenum lends itself to the estimation of duodenal pathologic conditions, especially in cases in which there is a stenosis or interference with the peristalsis. It will usually be found that a peristaltic wave will not pass over an erosion or ulcerated area of the duodenum; rather will it incite a spastic contraction at the site of the ulcer. For outlining the head of the pancreas this method of filling the duodenum would be quite useful, as the bismuth-filled duodenum encircles the head of the pancreas.

Fig. 2.—Patient in second position on apparatus.

CONCLUSIONS

We have been able to estimate a mechanical diagnosis of duodenal ulcer on the following: When a bismuth-and-water suspension is swallowed by a fasting patient, it readily passes the pylorus into the duodenum (because the acid stomach content is not taken up as when food is offered the stomach, neither is there a closure of pylorus as when a food bolus is swallowed). The stomach appears normal after the ingestion of a bismuth meal (2 ounces of bismuth oxychlorid to 13 ounces of porridge of one of the prepared wheat breakfast-foods), but there is a vigorous peristalsis and a rapid emptying of the stomach in as short a time as one-half hour and at least in two hours. The duodenum seems to be sluggish and casts a shadow for a longer interval than usual, but the food

rapidly traverses the remaining portion of the small intestines. By this method of filling the duodenum, as described above, the duodenum may present an hour-glass contraction at the site of the ulcer. Usually the duodenum is sluggish and does not exhibit any pronounced peristalsis. When the duodenum is filled and pressure is made at the outer curve of the duodenum as shown by the shadow, the patient usually experiences some pain or discomfort. We place the greatest weight on the rapid emptying of a stomach that exhibits the usual normal J-shaped shadow and a vigorous peristalsis.

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AMEBOID MOVEMENTS IN MACROCYTES AND MEGALOBLASTS *

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Since the observations made by one of us[1] of ameboid movements in a megaloblast, the opportunity has presented itself to study the fresh blood of five severe anemias.

In three of the bloods examined by us, ameboid motion was striking not only in many of the megaloblasts but also in the macrocytes. The absence of ameboid activity in the two remaining cases was probably attributable to the almost complete lack of unusually large cells in the blood. (For the blood findings, see the accompanying table.)

Two of the bloods (Cases 1 and 2) were demonstrated to the class and the changes described below were observed by practically all of the ninety-odd students. In addition, we made prolonged observations on each of the bloods. Our specimens were sealed at once with petrolatum to prevent drying and to avoid currents in the plasma as far as possible.

In Case 1, preparations of the blood were studied during a megaloblastic crisis. The megaloblasts were quite numerous and were so frequently irregular in outline that they were found without difficulty with low magnification (Leitz ocular No. 3, objective No. 3). When examined under the oil immersion they often showed a striking change in form (Figs. 1-3, 7-10, 13-17, 18-22, 23-34, 51-66, 67-97, 103-105, 126-138), and at times, though not often, the change was so rapid that the successive alterations in shape could not be sketched. The phenomenon consists essentially of a change in form due (1) to small, often numerous, serrations in the outline of the cell which may later be smoothed out or which may develop into a large, prominent projection or pseudopod; or (2) to the protrusion of one or more blunt, rounded pseudopodia, often large, which may be accentuated by a constriction at the base; or (3) to a combination of these appearances at one time in the same cell. At times rather deep indentations appeared at one or more points on the rim of the cell. Sometimes these nicks appeared to be bridged over in part by a delicate, colorless film, showing at times a slight wrinkling, as if the coloring-matter were at this point retracting

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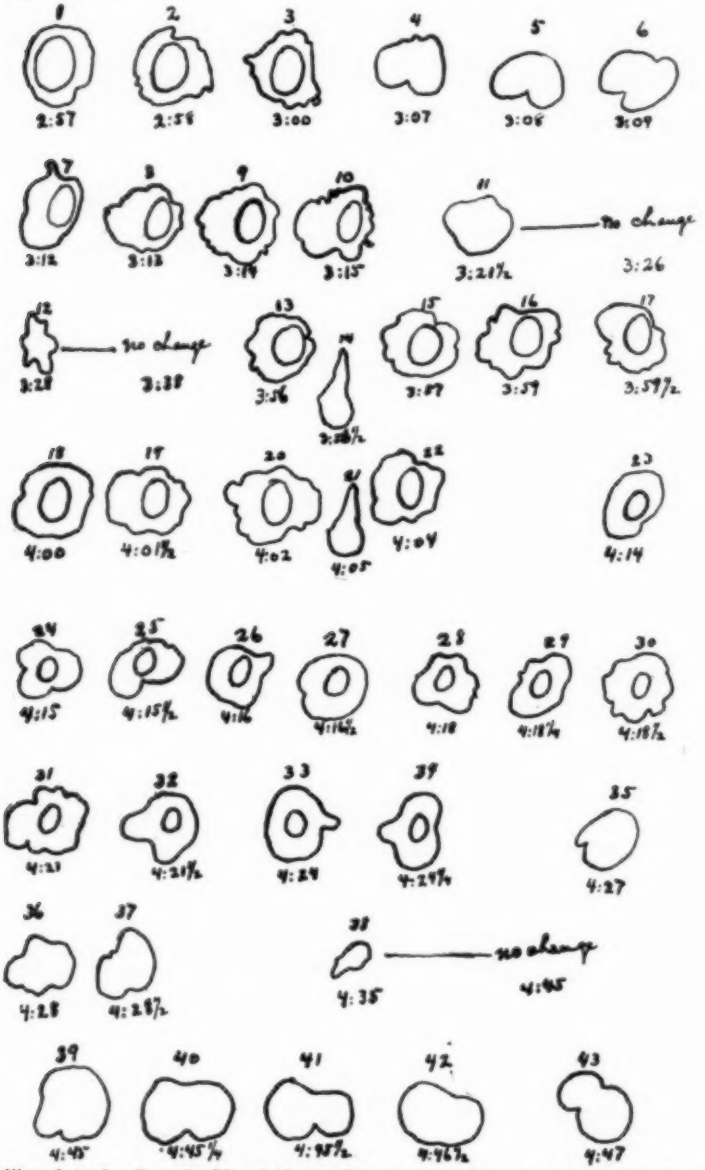
1. Thayer, W. S.: The Ameboid Activity of Megaloblasts, THE ARCHIVES INT. MED., 1911, vii, 223.

All drawings are made from specimens of fresh blood with Leitz ocular No. 3, objective 1/12" oil immersion. The drawings are not made to scale. The numerals above each sketch denote the number of the sketch; those below, the time intervals.



Figs. 1 to 3.—Case 1—Megaloblast. Figs. 4 to 6.—Case 1—Macrocyte. Figs. 7 to 10.—Case 1—Megaloblast. Fig. 11.—Case 1—Macrocyte. Fig. 12.—Case 1—Poikilocyte. Figs. 13 to 22.—Case 1—Megaloblast. Figs. 14 to 21.—Case 1—A poikilocyte which showed no change during time of observation. Figs. 23 to 34.—Case 1—Megaloblast. Figs. 35 to 37.—Case 1—Macrocyte. Fig. 38.—Case 1—Poikilocyte (small). Figs. 39 to 45.—Case 1—Macrocyte.

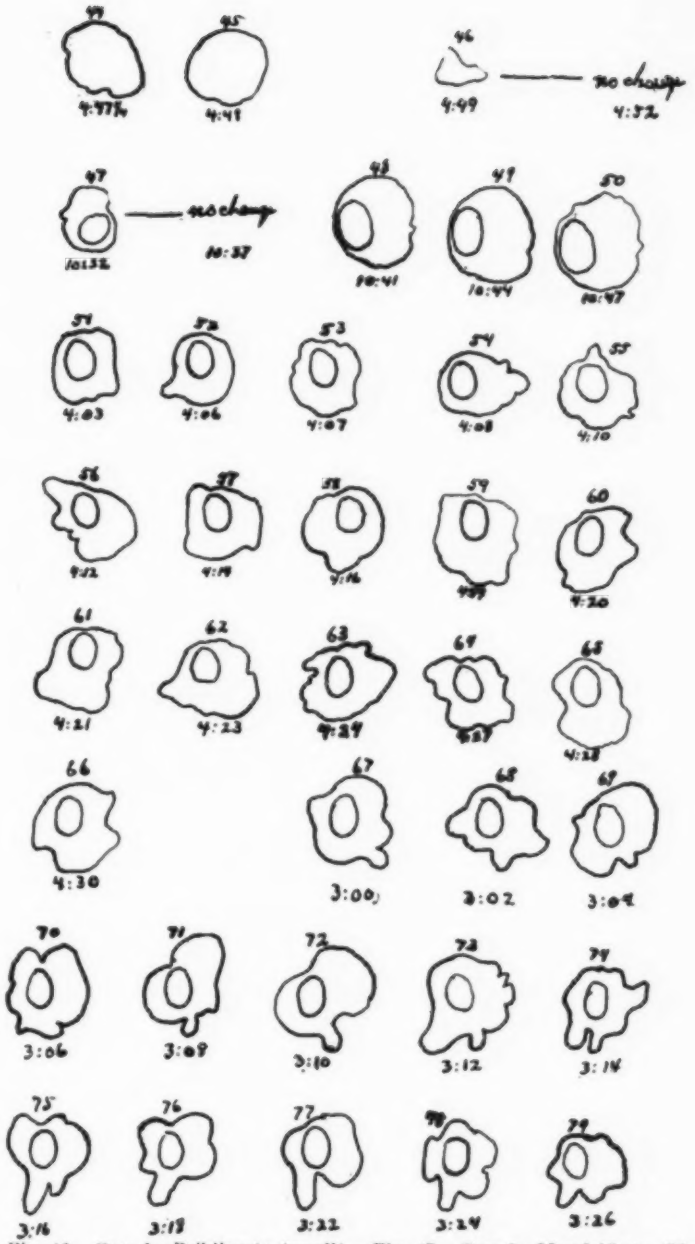
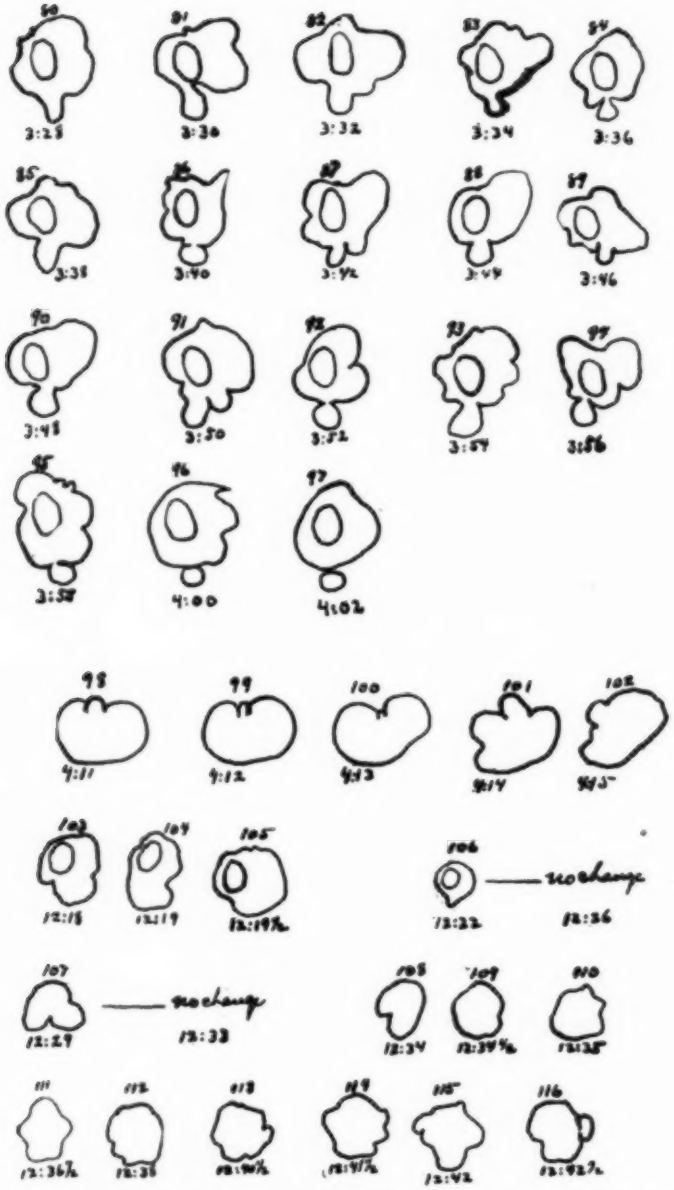
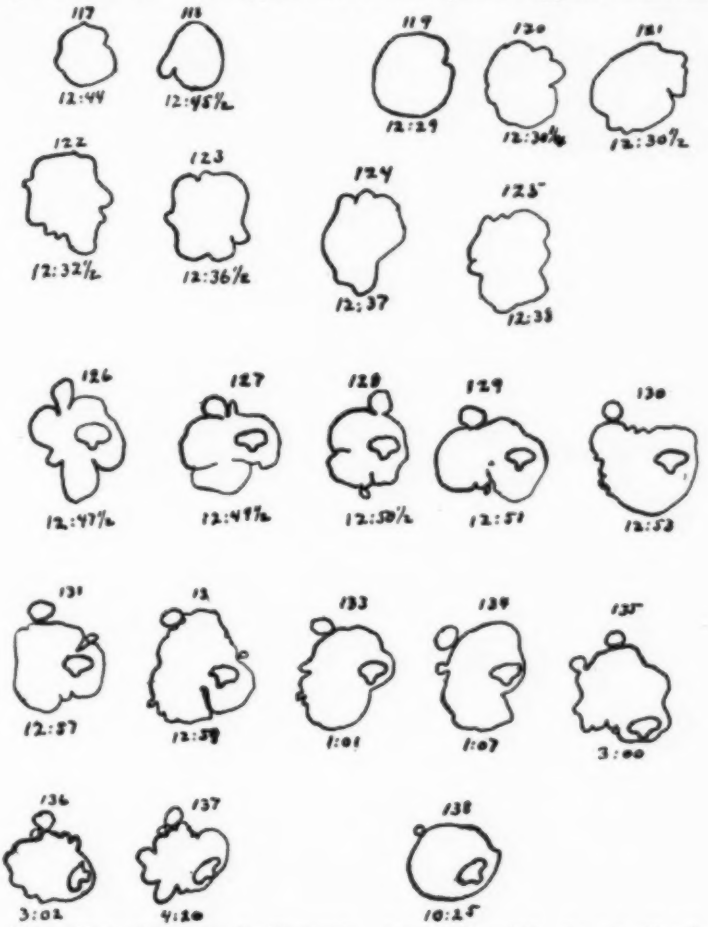


Fig. 46.—Case 1—Poikilocyte (small). Fig. 47.—Case 1—Megaloblast. Figs. 48 to 50—Case 1—Megaloblast. Figs. 51 to 66.—Case 1—Megaloblast. Figs. 67 to 97.—Case 1—Megaloblast.



Figs. 98 to 102.—Case 1—Macrocyte (rather small). Figs. 103 to 105.—Case 2—Intermediate. Fig. 106.—Case 2—Normoblast. Fig. 107.—Case 2—Poikilocyte. Figs. 108 to 112.—Case 2—Macrocyte. Figs. 113 to 118—Case 2.—Macrocyte.

from the stroma. Indentations such as these were often obliterated by very sudden movements, the colored substance springing back instantaneously and restoring the former contour of the cell or even forming a slight protrusion. The appearance at these points suggested somewhat



Figs. 119 to 125.—Case 3—Macrocyte. Figs. 128 to 138.—Case 3—Megaloblast. Fig. 138.—Case 3—The cell shown in drawings 126 to 137, the following morning.

the appearance of some infected corpuscles in estivo-autumnal malaria in which the brassy-colored protoplasm recedes from the colorless outline of the cell. The malarial cells are, however, often deformed and obviously degenerated. But these motile elements showed no abnormal

change in color or general appearance. No cell, indeed, with a suggestion of crenation or of the ordinary changes of shape observed in poikilocytes showed ameboid motion.

We have not been able to demonstrate propulsive motion in an ameboid cell, which remains practically in the same relative position during several hours' observation. In this respect the ameboid movement of the megaloblast differs from that often seen in the leukocytes. Indeed, the megaloblast protrudes its pseudopodium, only to retract it again. Inclusions or other evidences of phagocytosis in megaloblasts have not been seen.

Examination in Case 2 revealed the identical conditions observed in Case 1. Typical megaloblasts are not abundant, but normoblasts and intermediates are numerous. It is noteworthy that it is only the larger cells (megaloblasts and intermediates) which have shown unquestionable changes of form. In normoblasts (Fig. 106) we have not seen such alterations, though they have been looked for with considerable patience. Again, in Case 3, ameboid activity was very striking in the megaloblasts. Not all megaloblasts, of course, exhibit ameboid activity; and this is quite what one would expect from analogy with the leukocytes, some being inactive, others active.

That it is the large cells which are chiefly concerned in ameboid movements we have just seen. Further evidence in support of this fact is furnished by the results obtained in Cases 4 and 5. Here, though the reductions in the number of erythrocytes were quite as great or even greater than in the preceding cases, the absence of very large red corpuscles was conspicuous. In Case 5, in fact, no megaloblasts were seen at any stage of the disease, and they were scanty in Case 4. In neither of these cases was active ameboid motion demonstrable in the red cells.

AMEBOID ACTIVITY IN MACROCYTES

The observations just recorded confirm the findings previously reported.[1] In addition, we have observed exactly the same changes in shape in *macrocytes* (Figs. 4-6, 35-37, 39-45, 98-102, 108-112, 113-118, 119-125). The rapidity of change may be quite as great as in the nucleated red corpuscles and may present all the variations observed in the latter. There was no discoverable difference in kind or in degree. As in the case of the megaloblasts, not all of the macrocytes exhibit ameboid movements (Fig. 11). That non-nucleated cells should do so at all seems strange. But if the motility of the megaloblasts is in reality ameboid—and to the writers there appears to be no other explanation—then there can be no doubt that certain macrocytes, too, are possessed of it. Numerous ameboid macrocytes were observed in the blood of Cases 1, 2 and 3. A single, sluggish, rather small macrocyte was found in Case 5 in the

examination of many specimens, this cell appearing at the time of the blood crisis.

To determine the effect of temperature, specimens were examined on the warm stage at body heat. It was impossible to see any difference in the ameboid activity of cells studied in this way and those at room temperature (about 70 F.).

Two specimens from Case 1 were allowed to stand over night, the one in the incubator at 37 C., the other at room temperature, both sealed, as in all instances, with petrolatum. On reexamination, about twenty hours after the specimens had been prepared, it was found that the red corpuscles were remarkably well preserved, little, if any, laking having occurred, though there were crenation in a few cells and endoglobular degenerations in many. The most striking fact noted was that it was no longer possible, as it had been when the smears were fresh, to select megaloblasts with low magnification, since nearly all of them were now circular or oval in outline and therefore less conspicuous. A sluggish, almost imperceptible change in form was observed in one megaloblast (Figs. 48-50), and in one only, though many megaloblasts and macrocytes were watched over considerable periods of time. In Case 3, in a specimen of blood which had been prepared and sealed at 11 a. m., a megaloblast, actively ameboid, was fixed in the field at about 12:45 p. m. It remained very active until 4:20 p. m., when the observations were temporarily interrupted. The following morning at 10:25, the cell was almost round (Fig. 138) and the ameboid activity had entirely ceased. This megaloblast showed no endoglobular degeneration and no apparent loss in color. Its nucleus, as is the rule in such cells, showed practically no change in shape throughout the observations (Figs. 126-138). In these specimens examined after twenty or more hours, the leukocytes also showed a cessation of ameboid activity, though, unlike the red corpuscles, they frequently retained their irregular shape.

The cells, both megaloblasts and macrocytes, exhibiting ameboid movements were for the most part well colored, many seeming to be richer in hemoglobin than the average cell. A few, paler than the majority of the surrounding reds, were seen to change form, but no difference was determined in the motion of such cells and those more highly colored. No suggestion of crenation was observed in the ameboid cells. That the alterations in shape observed were not the result of osmosis is made probable by the absence of shadows or crenated erythrocytes in the neighborhood of those studied, and, further, by the fact that smaller red cells and many which were large remained immobile.

Many poikilocytes and normocytes were studied. In no case was there the least evidence of change in form while they were under observa-

tion. (Figs. 12, 14, 21, 38, 46, 107). Rolling of the cells was, of course, excluded. Currents were practically eliminated by sealing the specimens.

It occurred to us that it might be possible to demonstrate protoplasmic currents in the ameboid red cells by means of the so-called vital staining methods. It is the young cells which have shown ameboid activity and in these cells particularly, as Vaughan[2] and others have shown, the reticulofilamentous substance is demonstrable. The dyes used were Unna's polychrome methylene blue and neutral red in physiologic salt solution. Of the bloods possessing ameboid red cells, only that from Case 3 was studied in this manner. There was no difficulty in finding macrocytes and megaloblasts with well-stained reticula but in none of them could we see even a suggestion of ameboid movements, though control preparations made at the same time, unstained, contained very active ameboid cells. The neutrophilic leukocytes retained their ameboid activity well in the vitally stained specimens. Though our experiments with vital staining are limited to one case, it seems probable that the staining solutions used abolish the ameboid movements of red cells. This is all the more likely, since there is no description in literature of active movements of the vitally stained particles in erythrocytes, so far as we can discover.

The movements which we have described in macrocytes and megaloblasts were similar to those which were observed in the first case reported, but the protrusion and coalescence of small pseudopods were not so strikingly evident and the similarity of the movements to those of leukocytes not so apparent. The megaloblast originally described was a large, pale form, apparently a very immature cell, while, as has been said, these megaloblasts and macrocytes were all corpuscles of quite the normal color.

As a probable evidence of ameboid activity in megaloblasts, the occasional irregularity in outline seen in stained blood films may be recalled.

That ameboid activity in the red corpuscles may have considerable biologic significance is made clear by recalling the theories advanced to explain leukocytoses. It is not improbable that the "blood crises" are due to an active wandering out of the red cells from the marrow, the result of some unknown stimulus. Should this prove to be the case, it is likely that it will be found to be a departure from the normal, an unusual method of responding to increased normal or pathological stimulus, though for the fetus this may well be physiological. As yet, however, we have been unable to study blood from the fetus.

2. Vaughan, V. C., Jr.: The Appearance and Significance of Certain Granules in the Erythrocytes of Man, Jour. Med. Research, 1903, x, 342.

The counts given below coincide with the dates of examination.

CASE 1.—E. D. P., male, aged 41, white, med. No. 26,575, admitted to the hospital Nov. 22, 1910. Diagnosis: Pernicious anemia; erysipelas; streptococcus septicemia.*

Dec. 1, 1910: Blood examination:

Red blood-cells, 900,000.
Hemoglobin, 20 per cent.
White blood-cells, 8,100.

Differential count of 402 cells gave:

Lymphocytes	25.7%
Large mononuclears and transitionals	4.7%
Polymorphonuclear neutrophils	59.6%
Eosinophils	1.2%
Mastzellen	0.0%
Myelocytes, neutrophilic	4.2%
Unclassified	4.2%

In counting the leukocytes, 40 megaloblasts, 36 intermediates, and 24 normoblasts were seen.

The red cells showed marked anisocytosis and poikilocytosis. There were many large cells. The stained film revealed polychromatophilia, basophilic granulation, nuclear particles, and Cabot's ring bodies in large numbers. Marked signs of regeneration were, therefore, present.

CASE 2.—J. S., male, aged 17, colored, med. No. 26,868, admitted Jan. 25, 1911. Diagnosis: Severe anemia (pernicious?).

Feb. 21, 1911: Blood examination:

Red blood-cells, 1,750,000.
Hemoglobin, 38 per cent.
White blood-cells, 21,000.

Differential count of 800 cells gave:

Lymphocytes	24.7%
Large mononuclears and transitionals	8.7%
Polymorphonuclear neutrophils	59.0%
Eosinophils	6.3%
Mastzellen	0.7%
Myelocytes, neutrophilic	0.7%

Nucleated red cells were present in the proportion of 350 to 1,000 white cells, normoblasts predominating. There were considerable anisocytosis and poikilocytosis. Macrocytes were numerous but were not so large as in the preceding case. A Romanowsky stain showed much the same changes in the erythrocytes as in Case 1, but to a less degree, though the nucleated forms were more common.

CASE 3.—T. P. J., male, aged 43, white, med. No. 27,438, admitted May 28, 1911. Diagnosis: Pernicious anemia.

June 16, 1911: Blood examination:

Red blood-cells, 1,544,000.
Hemoglobin, 33 per cent.
White blood-cells, 3,200.

Differential count:

Lymphocytes	43.0%
Large mononuclears and transitionals	4.0%
Polymorphonuclear neutrophils	53.0%

*The infection occurred about one month after the present study of the blood was made.

Nucleated reds were present in the proportion of 230 to 1,000 leukocytes. Poikilocytosis and anisocytosis were marked, some of the cells being unusually large. The evidences of regeneration of the red cells were striking.

CASE 4.—H. M., male, aged 45, white, med. No. 27,336, was admitted May 4, 1911. Diagnosis: Aplastic pernicious anemia (autopsy).

May 4, 1911: Blood examination:

Red blood-cells, 1,280,000.
Hemoglobin, 20 per cent.
White blood-cells, 1,200.

Differential count of 100 cells:

Lymphocytes	60.0%
Large mononuclears and transitionals	17.0%
Polymorphonuclear neutrophils	16.0%
Eosinophils	0.0%
Mastzellen	1.0%
Myelocytes, neutrophilic	3.0%
Unclassified	3.0%

Two megaloblasts and one normoblast were found. The blood showed a considerable degree of anisocytosis and poikilocytosis but the absence of many macrocytes and, indeed, of any very large ones was striking, the morphology of the cells suggesting a severe secondary rather than a primary pernicious anemia, except for the megaloblasts. Aside from the scanty nucleated reds, there were no signs of regeneration in the red cells. The occurrence of myelocytes and a few nucleated red corpuscles indicates a futile attempt at regeneration.

CASE 5.—P. H., male, aged 56, white, med. No. 27,337, was admitted May 4, 1911. Diagnosis: Severe secondary (toxic) anemia (?), pernicious anemia (?). (The patient was employed in a dye factory and it is possible that the anemia was the result of his occupation; conclusive evidence is not yet at hand.)

June 7, 1911: Blood examination:

Red blood-cells, 900,000.
Hemoglobin, 15 per cent.
White blood-cells, 2,400.

Differential count:

Lymphocytes	37.0%
Large mononuclears and transitionals	3.0%
Polymorphonuclear neutrophils	57.4%
Eosinophils	2.0%
Mastzellen	0.0%
Myelocytes, neutrophilic	0.2%

No nucleated reds were found and there were no other evidences of regeneration of the red corpuscles. The absence of large cells is striking. Except for the lack of nucleated red cells and the presence of only slight poikilocytosis the blood bore a striking resemblance to that of Case 4. On vital staining with polychrome methylene blue, very few erythrocytes showed the reticulo-filamentous substance. After the red count had fallen to 530,000, defibrinated blood was given intravenously by Dr. W. L. Moss (who will include the case in a forthcoming report), and on June 13, 1911, an examination of the blood showed:

Red blood-cells, 1,580,000.
Hemoglobin, 19 per cent.
White blood-cells, 4,000.

There was now a normoblastic crisis, 143 nucleated red cells per 1,000 whites. No megaloblasts were found and the intermediates were small.

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THE EFFECT OF SOME HYDROTHERAPEUTIC PROCEDURES ON THE BLOOD-FLOW IN THE ARM *

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INTRODUCTION

It is generally agreed that therapeutic baths exercise a profound effect on the circulation of the blood. The exact changes, however, are not fully understood and this lack of knowledge is due to a number of causes. In the first place it is not easy to transfer the results of animal experiments to man because the skin vessels in the latter are more active and the temperature regulation more exact. In the second place alterations in the distribution of blood in the body, seemingly the most marked circulatory effect of baths, are not readily studied in man. The blood-pressure gives no definite information as to this distribution because the dilatation of one set of vessels may be neutralized by the constriction of another set, and the changes in pulse tracings are extremely difficult to interpret.[1] On the other hand, the plethysmograph which records the volume changes in an extremity and presumably the variations in the contained blood has added greatly to our scientific knowledge of the action of hot and cold water on the distribution of blood. Its use, however, is limited because it is necessary to keep the individuals extremely quiet during manipulations.

Considering the difficulties encountered in trying to obtain exact data, it is not surprising that frequent contradictions occur in the hydrotherapeutic literature concerning the effects of baths on the peripheral circulation. For this reason it seemed important to approach the subject from a new direction. We have therefore studied the effect of some representative hydrotherapeutic procedures on the blood flow in the arm, using a method recently described.[2] Many of our results correspond with those already obtained by the plethysmograph, but they are of interest because they are expressed in terms of blood flow. As has been indicated, the use of the plethysmograph is limited, as the individual must remain quiet during the observations and because the instrument cannot be taken off and replaced during an experiment. For this reason the reaction after a cold bath and the effect of exercise and friction cannot be studied by the plethysmograph, and our ideas concerning these have been deduced

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largely from such evidence as the sensations of the patient and the color and warmth of the skin. The method which we have used permitted a removal and a replacement of the instrument on the arm so that comparative records before and after treatments could be obtained. We have therefore been able to study the effect of exercise, friction and the reaction after cold baths.

EFFECTS OF LOCAL PROCEDURES

The application of hot or cold water to the arm is one of the simplest hydrotherapeutic procedures, and the effect of such applications on the local circulation has been studied by various methods. U. Mosso,[3] Sarah Amitin[4] and others have shown that in general the arm shrinks under the influence of cold and swells under the influence of heat. A. Mosso[5] has shown that the size of the volume pulse is diminished by local cold and increased by local heat, and Balli's[6] tachograms show similar changes. Lommel[7] has shown that the rate of propagation of the arterial wave is accelerated by local applications of cold. From these and other observations it has become generally accepted that the arteries and other blood-vessels in the extremities contract under the influence of local cold and dilate under the influence of local heat, and it has been assumed that the local blood-flow is lessened in the former condition and accelerated in the latter. Friedel Pick[8] has proved this for the legs of dogs by direct measurements of the venous outflow.

In order to study the effect of thermic stimuli on the local blood-flow, we have modified our method by partially filling the plethysmograph with water. The temperature of this latter could be varied by passing hot or cold water through an encased coil of block tin. Records of the blood-flow made at frequent intervals were compared with the temperatures of the water surrounding the arm.

It is well known that the volume of the arm often fluctuates considerably in the ordinary plethysmograph, and we found similar fluctuations in the rates of flow. Inaccuracies of the method undoubtedly accounted for many of the minor fluctuations. Others, however, were probably due to psychic or other nervous influences which, as Weber[9] and others have shown, exert a powerful influence on the caliber of the peripheral vessels. These nervous variations could usually be distinguished from those produced by thermic influences on account of their transient and variable character. They were most apt to be encountered when the blood-flow approximated the normal rate, and tended to diminish when the water surrounding the arm was either hot or cold. When both arms were studied, fluctuations were frequently encountered in the arm which was placed in an air plethysmograph and was not directly subjected to strong thermic stimuli. These observations are comparable to the experiments of Friedel Pick, who showed that when the leg of a dog was exposed to

hot or cold water the usual vasomotor effects of cutting or stimulating the sciatic nerve did not occur. The influence of strong thermic stimuli transcended the nervous influences.

The general qualitative effect of thermic influences on the local blood-flow in our experiments was very constant. Whenever definite results were obtained, heat always accelerated the local flow and cold always diminished it. A typical chart of this class of experiments is shown in Figure 1. It will be seen that the original rate of 3.7 c.c. of blood-flow per 100 c.c. of arm substance per minute when the arm was surrounded by water of 24 C. was gradually reduced by the cooling of the water until a minimum rate of 1.1 c.c. was obtained when the water temperature had fallen to 14.5 C. In all of our experiments a similar fall occurred but we were unable to use very low temperatures on account of the pain in the arm caused by the cold. On this account, perhaps, we obtained no increased flows at very low temperatures such as would correspond to the

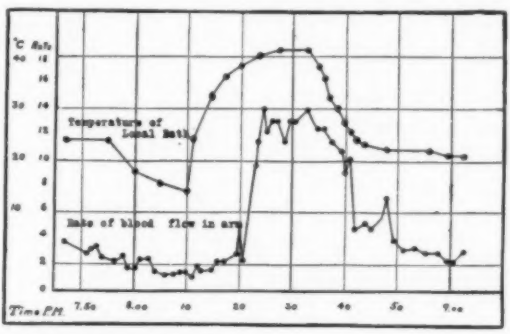

Fig. 1.—The effect on the local blood-flow of varying the temperature of the water surrounding the arm. Note that for corresponding temperatures the flow is more rapid when the temperature is falling than when it is rising.

swelling of the arm described by U. Mosso or to the relative increase of heat elimination described by Robinson and Stiles.[10] On this account also, perhaps, when the arm was again heated to a neutral temperature we obtained no excessive increases in the rate of flow such as one might expect from the changes in volume described by U. Mosso, or the changes in volume pulse pictured by A. Mosso. As a rule in our experiments the rate of flow did not immediately increase when the temperature surrounding the arm was raised, but remained relatively slower than it had been for corresponding temperatures when the temperature of the water bath was falling. Thus we obtained no records which could be interpreted as showing a "paralysis of the vessels" from cold.

High temperatures invariably produced a most marked acceleration of the rate of flow. This developed more suddenly in Figure 1 than in

most of our experiments; but there was nearly always a rapid increase in the rate of flow at about the time that the temperature of the water passed 35 to 38 C. The increases from the original rates to the maxima were always very marked, much more so than those which Friedel Pick obtained in dogs. The following figures give the rates per minute per 100 c.c. of arm substance before and after the application of heat: 3.7 c.c. to 14 c.c., 4 c.c. to 29 c.c., 6 c.c. to 22 c.c., 5 c.c. to 26 c.c., 3 c.c. to 26 c.c., 4 c.c. to 22 c.c., 6 c.c. to 45 c.c.

When the temperature of the water bath was again reduced after reaching temperatures of 42 C. to 50 C., the rate of flow always fell; but this fall never occurred promptly and for a given temperature of the arm bath the rate of flow was invariably faster than when the temperature was rising (Figs. 1, 2 and 3). Similar results published by U. Mosso for the volume changes in the arm were interpreted as indicating a vascular paralysis, a subject which will be discussed later.

Several causes contribute to produce the fluctuations in the rate of blood flow which follow the local applications of hot or cold water. It is difficult, however, to estimate the exact part played by each. Theoretically one may consider: (1) the direct action of heat or cold on the blood-vessels or their local nervous connections; (2) reflexes excited by thermic stimuli and acting on local vessels; (3) reflexes excited by thermic stimuli and acting on the vessels of the body in general; and (4) the effect of cooling or warming the blood. The separation of the first two of these or the local effects, from the last two or the general effects, can be accomplished by a simultaneous study of the two arms when only one of these is subjected to external changes in temperature.

Studies of this character have yielded very contradictory results. U. Mosso describes a single experiment in which the arm exposed to hot water became swollen while the opposite arm, exposed to an indifferent temperature, shrank. Sarah Amitin, in similar experiments, found that while the arm in hot water became swollen the opposite arm did not change volume. She found, however, that when one arm was exposed to cold water both shrank. Friedel Pick obtained unilateral effects in studying the action of thermic stimuli on the blood flow in the legs of dogs. On the other hand, many observers in recent years, notably O. Müller,[11] have emphasized the fact that the vessels in the two arms tend to act in unison when one is subjected to hot or cold applications. We have carried out several sets of experiments in which the rates of flow in the two arms were compared while one was exposed to hot or cold water and the other was in an air plethysmograph, and we are inclined to believe that the contradictory reports published by others may be explained by variations in the room temperature.

The first set of these experiments were made during the spring months of 1910, in a fairly warm room. During the application of heat to the arm, the body as a whole became warm and the individual perspired freely. Figure 2 shows the results obtained in one of the three experiments performed at this time, all with uniform results. It will be seen that the application of heat to the right arm caused an increased blood-flow in the left arm. In contrast with the right, however, this increase in the left took place somewhat later, did not reach the same high point, and the rate decreased more promptly when the right arm was cooled to

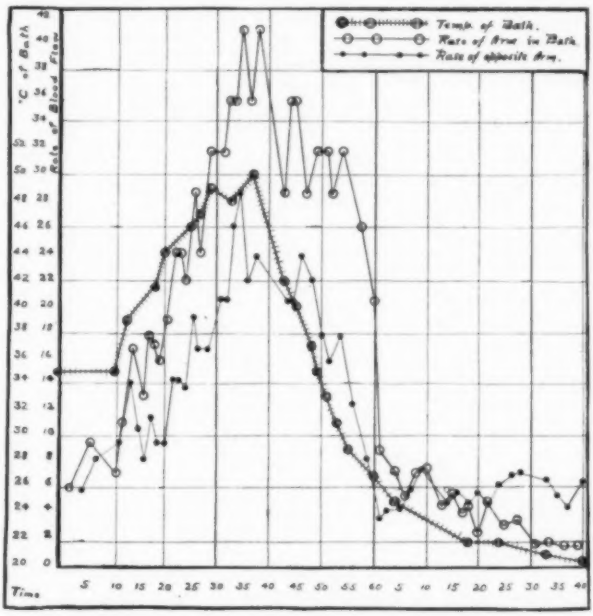

Fig. 2.—The effect of varying the temperature of the water surrounding one arm on the blood-flow in this and in the opposite arm, the room being warm. The right arm was exposed to the varying temperatures, the left was in an air plethysmograph. Note that when heat was applied the blood-flow in the latter rose later, did not reach the same high point, and fell more promptly. Also that when cold was applied the flow in the right arm fell below that in the left.

a neutral temperature. When the water was still further cooled (below 25 C.), the rate in the arm exposed to the cold diminished, while it remained approximately normal in the other. The marked discrepancy between these results and those of U. Mosso and of Sarah Amitin led us to repeat this experiment in a cold room, taking care that the individual should remain slightly chilly throughout. In Figure 3 it will be seen that under these conditions the arm directly exposed to the changing

temperature showed the customary changes in blood-flow while the opposite arm showed throughout a slow rate of flow, the maximum increase not being over twice the original rate. When the water in the plethysmograph was cooled, both arms showed an extremely slow and approximately equal blood-flow. The different results in these two experiments show clearly that the room temperature exercises an important influence on the distant vascular reaction when hot or cold water is applied to a limited part of the periphery. They also show that the local effects of such applications are largely independent of the general effects. O. Müller[11] also noticed that the temperature of the room disturbed the general effects, but in a somewhat different manner from what we have described. He states that when the temperature of the room was considerably below 20 C., the distant effects of cold were lessened and conversely when the temperature of the room exceeded 20 degrees the distant effects of local heat were lessened.

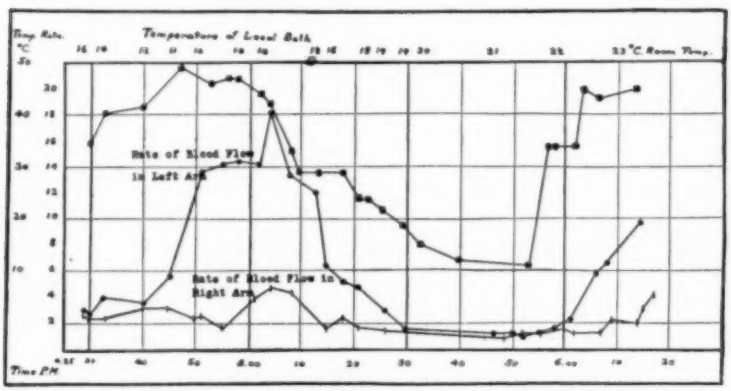

Fig. 3.—The effect of varying the temperature of the water surrounding one arm on the blood-flow in this and in the opposite arm, the room being chilly. The upper curve represents the temperature of the local bath, the middle the blood-flow in the arm to which the water of varying temperatures was applied, and the lower the blood-flow in the arm contained in the air plethysmograph. Note that heat increased the flow in the left arm very markedly while it did not greatly affect that in the right arm. At low temperatures both arms showed a very slow rate of blood-flow.

To demonstrate this more clearly a final experiment was performed, during which the room temperature and the temperature of the water about the arm were varied independently. During the first part of this experiment the room was kept at a constant temperature of 22 C. to 24 C., while the temperature of the water bath surrounding the left arm was raised from 32 C. to 41 C. The blood-flow in the left arm increased from an average of 5 c.c. per 100 c.c. of arm substance per minute, to

15 c.c., while the blood-flow in the right arm varied but little from the original rate of 4 c.c. During the second part of the experiment the temperature of the water bath was maintained at 42 C., while the temperature of the room was reduced from 24 C. to 12 C. In this period the blood-flow in the left arm fluctuated in the neighborhood of 16 c.c. while the blood-flow in the right arm fell from the neighborhood of 4 c.c. to about 2 c.c. During the third period the temperature of the water surrounding the left arm continued to be about 42 C. while the temperature of the room was raised from 12 C. to 30 C. In this period the rate of blood-flow in both arms increased. That of the left rose from 17 c.c. to 27 c.c.; that of the right from 2 c.c. to 7 c.c. During the fourth period the room was kept warm and the temperature of the water surrounding the left arm was reduced from 42 C. to 14 C. The rate of blood-flow in the left arm fell from 27 c.c. to 2 c.c., while that in the right arm fell from 7 c.c. to 4 c.c. In the final period the temperature of the room was again reduced to the chilling point and the rates in both arms fell still further, approximating each other at a little over 1 c.c. In this experiment the blood-flows in the arm exposed to the changing temperatures of the water followed these changes rather closely and were but moderately affected by the room temperature. The blood-flows in the opposite arm, on the other hand, depended chiefly on the room temperatures but was moderately affected by the changes in the temperature of the water surrounding the first arm.

Our experiments demonstrate that thermic stimuli produce both local and general effects on the peripheral blood-vessels. The former are shown by the facts that (1) when heat is applied the blood-flow is always relatively faster in the arm to which it is applied; (2) when the individual is kept cool or chilly, the rate in the opposite arm may not be accelerated; and (3) when cold is applied the blood-flow in the affected arm is often less than in the opposite arm. The effect of local applications on the blood-vessels of the opposite arm is indicated by the fact that the blood-flow in the latter frequently undergoes changes similar to, though usually not so great as, those which occur in the arm directly treated.

The factors causing the distant effects of heat and cold will be discussed later. Concerning their local action we have two possibilities. The first of these would attribute these effects to reflexes originating from the heated or cooled skin and acting on the local vessels. While it is possible that such reflexes occur, they do not seem to be necessary, for Friedel Pick observed characteristic changes in the blood-flow following thermic applications to the legs of dogs even after the sciatic nerves were cut. This seemed to indicate that thermic influences may act directly on the local nervous or vascular apparatus. Similar results have been obtained by others.[1]

When the arm is heated excessively, signs may appear which indicate a loss of contractile power on the part of the vessels. U. Mosso assumed the existence of such a "vascular paralysis" as the result of heating the arm, and based his assumption partly on the observation that after a thorough heating the vessels do not contract promptly when cold is applied. While our observations on the blood-flow confirm his, we are inclined to give them a different interpretation. The temperature to which the tissues are exposed is not the same as the temperature of the surrounding water bath. When the tissues are thoroughly heated the local blood-flow is markedly increased; the deep layers of the skin are relatively protected from the cold water bath, and one would not expect a sudden contraction following its use. Occasionally, however, the skin remains red for hours, even days, after exposures to very hot water. Furthermore, in several of our experiments the curves obtained after very hot water were peculiar in that only a small amount of blood could enter the arm at a uniform rate. To our minds this indicated that the vascular reservoir was diminished, and taken in conjunction with the fact that the rate was very fast and the arm red, it seemed to us probable that the vessels were dilated to their utmost and did not empty sufficiently between determinations to allow the reception of much more blood. This effect persisted for some time after the rate began to fall as a result of cold applications but ultimately completely disappeared. In such a case, and also where the the skin remains abnormally red, one might speak of a "vascular paralysis."

EFFECT OF GENERAL PROCEDURES

General hydrotherapeutic treatments are usually initiated by a hot procedure, such as an electric cabinet bath, and are usually terminated by a cold procedure, such as a cold shower. In some cases cold procedures alone are used. Exercise, friction, the mechanical action of douches, and the temperature of the room are important accessories. In the present study we have aimed to determine the effect of general hot and cold procedures on the circulation in the arm. We have also tried to outline the part played by some of the above named accessories. Finally, mouth temperatures have been taken during many of the experiments for the purpose of comparing these with the peripheral blood-flows and with the ability of the individuals to react. Prolonged cold and medicated baths such as are used in the treatment of fever and of heart disease were not studied.

SUMMARY OF EXPERIMENTS

A number of experiments were carried out, the results of which are shown below in the form of tables. A general discussion follows. Many details of the experiments have necessarily been omitted from the tables

such as, for example, the fluctuations in blood-flow caused by nervous influences or by errors in the method employed. Some idea as to the extent of these fluctuations may be obtained from Figures 1 to 4. When the fluctuations were very marked the figures given in the tables have been starred. When more or less continuous changes in rates occurred, especially after hot or cold procedures, the changes have been indicated by a dash connecting the earlier with the later rates. All temperatures have been expressed in the centigrade scale, and the blood-flows have been expressed in terms of the number of centimeters of blood entering 100 c.c. of arm substance per minute. The plethysmograph always included the hand, forearm and lower arm.

In the first set of experiments, represented in Table 1, the individuals were placed at rest in a bath tub, and the original rates were taken while the individuals were covered by a light blanket. Hot water (41 C. to 45 C.) was then run into the tub. This usually covered the lower extremities, the abdomen and parts of the chest and of one arm, leaving the arm in the plethysmograph outside of the water. The subjects were left in the hot water until a profuse perspiration occurred. After this the water was allowed to run out of the tub and a spray with tap water under high pressure and at a temperature of about 15 C. was given without moving the individual or the apparatus. The rates of flow through the arm were taken at frequent intervals throughout the experiments. In some instances the shower was repeated once or twice, but the results of these secondary showers are not charted in this table.

TABLE 1.—HOT TUB BATHS FOLLOWED BY COLD SPRAYS

Name	Room Temp.	Original Rate	Average Maximum Rate in Bath	Rate when Water Ran Out	After Spray	Maximum Mouth Temp. in Bath
Hew.	25 C.	3.3*	14.4	14.4	14.5	38.5 C.
Hew.	23 C.	...	20.0	16.0	14.	38.4 C.
Meg.	25½ C.	2.2	12.4	7.1	3.2	37.9 C.
Alex.	....	4.3*	20.0	13.0	5.4	37.9 C.
Sti.	24 C.	2.7	18.0	14.	4.3	....
Gan.	22 C.	2.2	22.0	10.	2.5	....
Sch.	21 C.	2.0	13.0	6.5	4.0	38.3 C.
Cha.	21 C.	2.0	14.	2.2	2.0	38.1 C.
Lot.	23 C.	2.0	11.0	10.1	3.6	....

In the experiments shown in Table 2 the same procedures were used except that in place of hot water the individual was surrounded by numerous blankets which were heated by an enclosed set of incandescent lamps. The direct rays from the lights did not reach the skin. The "after spray" rates were taken as in the previous set of experiments. The individual then took an ordinary cold shower, dried himself and dressed. The rates after these procedures are given in the last column.

TABLE 2.—HOT AIR BATHS FOLLOWED BY COLD SPRAYS

Name	Room Temp.	Original Rates	Average Maximum Rates	Rates when Blankets were Removed	After Spray	Highest Mouth Temp.	After Ordinary Shower
Hew.	21 C.	6.5	10.0	6.0	5.0	37.2 C.	7.4
Hew.	26 C.	5.7	12.	10.0	4.3	37.5 C.	4.2

In Table 3 the individuals were placed at rest in a tub, and the shower was given without any preliminary heating.

TABLE 3.—COLD SPRAYS WITHOUT HOT PROCEDURES

Name	Room Temp.	Rates Before Shower	Rates After Shower	Rates After Dressing
Lot.	23. C.	1.4	1.3	1.8
Lil.	23.5 C.	2.6	1.3	2.5

Two objections may be raised to the results obtained in these experiments. In the first place the arms from which the observations were taken were kept continuously in the air plethysmograph and did not come in contact with the hot or cold water. In the second place important accessories to a therapeutic treatment were absent, such as the exercise taken during or after the bath and the local friction from douches and from rubbing with hands or towels.

Table 4 shows the results obtained during observations made on patients of the psychopathic hospital who were taking baths for therapeutic purposes. We were permitted to make these observations through the courtesy of Dr. A. M. Barrett. In these cases rates were taken before the electric cabinet bath, after the electric cabinet bath, and finally after cold procedures which consisted of gradually cooled showers and douches.

TABLE 4.—ELECTRIC CABINET BATHS FOLLOWED BY COLD SHOWERS

Name	Average Room Temperature	Original Rates	After Coming Out of E. C. B.	After Cold Procedures	Highest Mouth Temperatures
Smi.	26 C.	6.7	10.0	8.5	37.5 C.
Schu.	24 C.	4.7	11.5	4.5	37.7 C.
Wood	24 C.	5.3	10.0-6	5.2	37.3 C.
Per.	24 C.	5.0*	11.0	5.2*	37.5 C.

In Table 5 are recorded the effect of cold showers as ordinarily taken by vigorous young adults. The rates were taken before undressing, after undressing and finally directly after drying, the individual being lightly covered with a blanket.

TABLE 5.—COLD SHOWERS

Name	Room Temperature	Dressed	Undressed	After Shower	Mouth Temperatures Before	Mouth Temperatures After
Hew.	25 C.	6.2	6.7	4.4-5.8	37.0 C.	36.6 C.
War.	25 C.	2.0	2.4	5.9	36.7 C.	37.2 C.
Hoy.	25 C.	2.6	3.8*	4.1	37.0 C.	36.9 C.

In these last two sets of observations the apparatus was taken off and applied several times. The cold procedures were accompanied by considerable exercise and were followed by a vigorous rubbing with a towel. While it was impossible to obtain as many records in these cases, and while the immediate effects of procedures could not be followed, yet they represent more accurately the changes which occur in practical bath treatments.

EFFECT OF HOT PROCEDURES

As hot procedures, the full tub bath, the hot air bath and the electric cabinet bath were used and these were continued until the individuals perspired profusely. During these applications of heat the mouth temperatures invariably rose. During the hot air and the electric cabinet baths, the mouth temperatures rose to at least 37.2 C., and usually to 37.5 C. or 37.7 C. In the full tub baths the individuals were partly covered with hot water (41 C. to 43 C.), and the body temperatures usually rose above 37.8 C. and frequently above 38 C. During these hot procedures the rate of blood-flow through the arm invariably increased, never being below 10 c.c. per 100 c.c. of arm substance per minute, and often exceeding 20 c.c. These rates were from two to ten times the original rates, but this ratio seemed to depend more on the original than on the final rate. The flow increased, even though the arm itself was not directly exposed to high temperatures. While in general the acceleration of flow was greater when the mouth temperature was high, there seemed to be no strict parallelism between the two.

When the hot procedures were over and the individuals were exposed to ordinary room temperatures, a fall occurred in the rate of blood-flow through the arm, usually reaching 70 per cent. or less of the highest previous rate. In one patient (Table 1 Cha.), who was quite unaccustomed to baths, the rate rose during the hot tub bath from 2 c.c. per 100 c.c. of arm substance per minute to 14 c.c., but it fell to the original rate when the hot water was let out of the tub. The body temperature at this time was 37.8 C., and we regarded this abrupt fall as pathological. The results obtained on the patients of the psychopathic hospital (Table 4) showed rather less than the customary accelerations of blood-flow after the electric cabinet bath. Two causes contributed to produce this result. One was the initial warm temperature of the room, which gave these patients relatively rapid rates before entering the cabinet. The other was the fact that our apparatus was reapplied after the patients had come out of the cabinet, and that during the elapsed time the rates probably fell below what they had been in the cabinet.

EFFECT OF COLD PROCEDURES

The effect of simple cold procedures following the hot procedures was quite uniform in that they always caused a fall in the rate of flow through the arm. The extent of this fall varied greatly. In some the cold reduced

the flow to less than the original rate while in others the reduction was much less marked, and the flow was left considerably above the original, though usually below that produced by heat. In a general way, when no exercise was taken and no friction was given, the rate of blood-flow was more apt to remain above the original rate if the body temperature had been much elevated by the preceding heat. In such cases the individuals usually took the cold showers with ease and were left warm and exhilarated, reactions being obtained without exercise or friction.

When primary cold procedures were given without exercise and without friction, or when repeated cold procedures without these were given after hot ones, the rate of flow through the arm was reduced by each shower. This result was obtained both when the arm studied had been directly exposed to the cold water and when it had been protected by being enclosed in the plethysmograph.

Attempts were made repeatedly to obtain records during the cold showers but the results were rather unsatisfactory, partly on account of involuntary movements of the individual and partly because it was difficult to protect the plethysmograph from the cold spray which caused the enclosed air to shrink. We frequently gained the impression, however, that the flow during the shower was somewhat slower than it was a few minutes later.

EFFECT OF VARIATIONS IN BODY TEMPERATURE

Warm procedures invariably raised the mouth temperatures to some extent. In our experiments this was most marked in those taking hot water tub baths which usually raised the temperature to 37.9 C. or over. When hot air or electric cabinet baths were used, the rises in temperature were less marked but the mouth records often exceeded 37.5 C. The more marked effect of hot water baths is due in part to the high specific heat of water but still more to the fact that they prevented evaporation from the portions of the body immersed in water so that the individuals lost this method of maintaining their normal temperatures. During cold procedures the body temperatures were not reduced below the normal in a large number of therapeutic treatments studied, but when cold procedures were given without following the customary rules of hydrotherapy, it frequently happened that the mouth temperatures fell below 36.7 C.

To what extent do these variations in the body temperature influence the blood-flow in the arm and the various phenomena accompanying hydrotherapeutic treatments? The effect of the body temperature is naturally a general one and not dependent on the point at which the thermic application is made. It must, therefore, be distinguished from the local effect of hot or cold water which usually exceeds the distant effects. It would seem from experimental evidence that such distant effects of hot procedures may be produced either by reflexes excited by

stimulation of the thermic sense organs in the skin[12, 13] or by changes in the temperature of the carotid blood which supplies the brain.[14] The relative importance of these factors in producing the circulatory changes of man during the therapeutic use of water has not been carefully studied by scientific methods, though recent writers[11] have usually assumed that distant effects are caused by reflexes arising from the cutaneous thermic sense organs and acting on the peripheral vessels by way of the vasomotor center.

Several facts indicate that the body temperature is a factor which cannot be neglected in this connection. The ordinary measures used in therapeutic institutes for hydrotherapy emphasize the importance of preventing heat losses from the body. The rooms are kept unusually

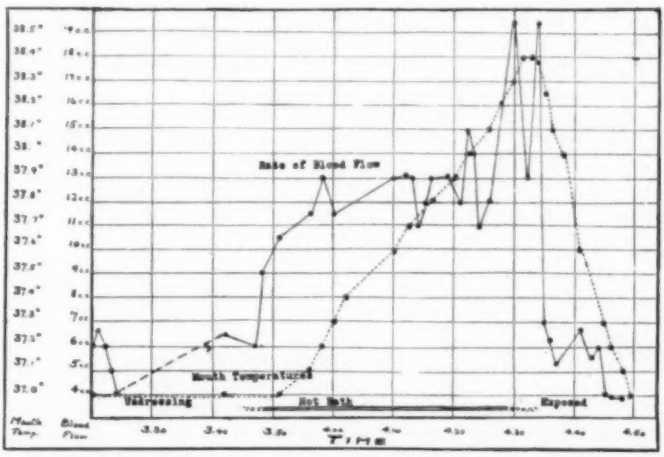

Fig. 4.—The relation between the mouth temperature and the blood-flow in the arm during a hot tub bath. Note that the rate rose at the beginning of the bath before the mouth temperature showed a change; also that the rate fell when the water ran out while the mouth temperature was still above 38 C.

warm, the cold procedures are short, and individuals not accustomed to baths are given preliminary hot procedures. In our experience when the body temperature is reduced, cold procedures are apt to leave the individuals chilly and with a slow peripheral rate of flow. After hot water baths, on the other hand, where the body temperature is considerably elevated, cold procedures are borne unusually well, even though the room is cold. The one exception to this rule which we observed (Cha., Table 1) was regarded as a pathological chilling on exposure to a cool room after a warm procedure.

In order to study more accurately the relation between the effect of thermic stimuli and the effect of body temperatures, two experiments

were performed in which an effort was made to distinguish these factors. The experiments were performed in a cool room (18.5 C.); the individuals were given hot tub baths, and the body temperatures were raised to about 38.4 C. The water was then run out of the tub and the individuals left exposed to the cool air of the room until the mouth temperatures fell to normal. A series of readings were made of the mouth temperatures and of the rates of flow through the arm. Essentially the same results were found in both experiments but the more striking of the two are shown in Figure 4.

In Figure 4 it will be seen that the original rate of about 6 c.c. fell under the influence of a cool room and partial exposure to 4 c.c. The individual then undressed and was covered with a light blanket, the rate at the end of this being 6.5 c.c. The tub was filled with water of a temperature of 41.7 C., and the rate of blood-flow rose almost immediately to above 10 c.c. This change occurred before any rise in the mouth temperature was recorded. As the body temperature rose, the rate of blood-flow took a slightly higher level and finally with the body temperature of 38 C. the blood-flow reached a high mark of 19 c.c. In the other experiment this secondary rise of blood-flow did not occur. When the water was run out of the tub and the individual was exposed to the cold air of the room, the rate of blood-flow fell almost immediately to the neighborhood of 6 c.c., although at this time the mouth temperature remained above 38 C. A marked fall in blood-flow did not occur until the temperature reached 37.3 C., when the rate fell somewhat below the original rate.

In these experiments we have a clear demonstration that the rate of blood-flow in the arm which was kept continuously in the air plethysmograph varied independently of the body temperature. The rate increased promptly when the body was covered with hot water and before the body temperature was raised and it fell promptly when the water was let out, although the body temperature remained high. We believe, however, that the experiments also showed a definite effect of the elevation of body temperature. From our experience, naked exposures to a room temperature of 18.5 C. should send down the rate much more than what was found seven minutes after the hot bath.[15] It seems probable that the elevated body temperature prevented a still further fall of blood-flow. In contrast to these observations we have noted on several occasions that when the body temperature was slightly subnormal, exposure to a cool room almost immediately reduced the flow to the neighborhood of 1 c.c., and the individual became very chilly. We believe that these experiments indicate that while the external temperature exercises a more powerful effect on the peripheral blood-flow than does the body temperature, the effect of the latter should not be neglected. In practical hydrotherapy the

slight elevations of temperature caused by the hot procedures, and the avoidance of excessive heat losses tend to prevent the excessive constriction of the vessels with chilling which are apt to follow exposure to cold air or cold water if the body temperature is normal or subnormal.

THE EFFECT OF EXERCISE AND FRICTION

We have already stated that in our experiments, cold procedures without exercise or friction were invariably accompanied by a fall in the rate of flow through the periphery (Tables 1, 2 and 3). This occurred even though the spray did not last long and even though the subjects felt exhilarated and not chilly. Similar results were obtained when the arm was taken out of the plethysmograph and directly exposed to the spray.

In Table 5, however, it will be seen that in two of three individuals a primary cold bath was followed by an acceleration in the peripheral rate of flow. Similar results were obtained on several occasions at the end of long tub experiments when the individual took a final cold shower with exercise and rubbing. (See for example the first experiment in Table 2.) It would appear from a comparison of our results that when an acceleration of flow occurs after primary cold procedures, it is due to the exercise and friction with which these are accompanied. This was especially noticeable in Table 5, War., who showed the most marked increase of flow, was unaccustomed to showers, took a very short one, and exercised vigorously. The difference in our results may have been due in part to the fact that where the arm was kept continuously in the plethysmograph careful drying was not attempted and the rate was held down by the wet condition of the skin. Under any circumstances, it is certain that primary cold procedures never accelerate the rate of flow through the arm to the same extent as do hot procedures. In some cases a moderate acceleration is obtained; in others the rate is not much changed. When, however, the cold is given without friction, exercise and drying, the rate of flow invariably falls as a result of the procedure.

THE REACTION

The reaction after cold procedures plays an extremely important part in practical hydrotherapy. The patient is said to react well when he feels exhilarated and warm and when the skin becomes pink. The absence of these — but especially the sense of chilliness — constitutes a failure to react. It is not always easy to define a reaction. This is especially true when the individual feels exhilarated and warm immediately after the cold procedure but becomes chilly on the least exposure or spontaneously within the next half hour or so. The conditions which are used to favor reaction are preliminary hot treatments, warm rooms, short cold procedures, and the use of exercise and friction.

In our experience, decided failures to react are always associated with a slow peripheral rate of flow. This was seen especially in those experiments where successive sprays were given to individuals who had been heated by a hot tub bath. In these cases the chilliness indicative of the failure to react always occurred when the blood-flow in the arm had become unusually slow. On the other hand, even a fairly typical reaction was not necessarily accompanied by a fast rate of blood-flow through the arm. In some cases (Table 2) the rate fell after a cold spray and yet the individuals gave the appearance and had the sensations of fair reactions. In such cases the red color of the skin must have been a purely local phenomenon and not associated with a dilatation of the deeper vessels. Usually the best reactions were seen when the rate of blood-flow did not sink much below the original rate, and quite frequently it was moderately elevated during the reaction. Our experiments seem to dispose finally of the old views of Winternitz which have been subjected to a destructive criticism by Matthes,[1] concerning the effect of cold and heat on the blood-flow in the arm. Winternitz believed that heat caused a "passive" dilatation of the vessels with slowing of the blood-current. Numerous physiological experiments as well as our observations on man have shown that heat markedly accelerates the rate of blood-flow in an extremity. The effect of cold, however, is more complicated. It is well recognized that under ordinary conditions cold contracts the blood-vessels and lessens the blood-flow. When intense cold is applied for some time, as in the case of an ice-bag, it causes a redness due to a dilatation of the local capillaries. We are unable to say whether this is accompanied by an increased flow or not. Furthermore, in the reaction after cold procedures it has been assumed that there is dilatation of the blood-vessels, and Winternitz went so far as to state that this "active" dilatation, in contradistinction to the dilatation caused by heat, is accompanied by an increased flow. Our experiments indicate that while the blood-flow may be increased during reaction this is never very marked and it is never increased to the same extent as it is during hot procedures.

On the other hand, we frequently obtained the impression that a secondary dilatation of the blood-vessels may occur following cold procedures independently of the immediate effect of exercise and friction, though it was difficult to be certain that this dilatation did not result merely from the cessation of the cold stimulus. In one case (Table 5, Hew.), however, we had an unusually clear association between the glow of a reaction and an increase in the rate of blood-flow. In this experiment the original rates of flow varied from 5.5 c.c. to 7.2 c.c. Immediately after undressing a rate of 6.7 c.c. was obtained, but a cold draft from the room in which the cold shower was running caused a momentary chilliness with reduction of the rate to 4 c.c. An ordinary cold shower was then

taken, following which the individual dried himself, returned to the tub, and was loosely covered with a dry blanket. The rates of flow taken immediately after were 4.8 c.c. and 4.2 c.c., and at this time he still felt a little cold from the water. After the second determination a feeling of warmth was experienced, and with this the rate of flow increased to 5.6 c.c. and 6 c.c. In this case the feeling of warmth and the increased rates were not due to the immediate effect of exercise or friction because they occurred when the individual was at rest. This glow with normal or somewhat increased rate of flow may occur even though the body temperature is subnormal. We were able to demonstrate this repeatedly when cold showers with exercise and friction were taken at the end of long tub exposures. While it is possible thus to raise the rate by the ordinary cold shower in vigorous individuals with subnormal temperatures, and while at the time these individuals often feel momentarily exhilarated and warm, it was noticed repeatedly that they were at the same time very sensitive to chilling influences and that a slight draft would cause a chilling sensation with a marked slowing of the rate. It was also noticed that when these individuals remained quiet in a room of ordinary temperature the glow was apt to be followed by chillness. It seemed to us therefore that while a momentary reaction may be produced when the body temperature is subnormal, such a reaction is apt to be fleeting and followed by chillness on slight exposure.

Our experiments support the general practice in hydrotherapeutic rooms of preventing such heat losses that the body temperature is lowered. Even when this is done, some individuals (Table 1, Cha.) may chill when exposed to cold air or cold water. The ideal conditions for a reaction after cold are attained when exercise and friction are used, the room is warm, and the body temperature is not allowed to fall below the normal.

CONCLUSIONS

1. When hot water is applied to the arm, the local rate may be increased from four to eight times, and when cold is applied the local rate may fall to one-half or one-fourth of the original.

2. These variations are often associated with similar, though less-marked changes in the blood-flow in the opposite arm. The latter is also influenced by the room temperature and the chillness or warmth of the individual.

3. A diminution of the contractile power of the vessels may occur after exposure to excessively hot water.

4. General hot procedures cause a marked acceleration in the blood-flow through the arm, and general cold procedures without exercise, friction or drying decrease the blood-flow in the arm.

5. When exercise, friction and drying are given with cold procedures, the slowing may be more or less neutralized and the rate may even be raised somewhat above the original.

6. Acceleration of blood-flow in an arm not directly exposed to the hot procedure is due in the main to reflexes excited by thermic stimulation of the cutaneous sense organs. The rise of body temperature, however, tends to prevent an excessive contraction of the peripheral vessels when the individual is exposed to cold.

7. If the body temperature is subnormal an immediate reaction may follow cold procedures which are accompanied by friction and exercise, but the individual is liable to become chilly later.

8. Reactions are usually, but not necessarily, accompanied by normal or moderately increased rates of flow.

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AN INVESTIGATION OF THE DEPRESSOR ACTION OF PITUITARY EXTRACTS *

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I. INTRODUCTION

It is generally conceded that intravenous injections of the extract of the infundibular portion of the pituitary gland cause a rise in blood-pressure; that this rise is due to a peripheral constriction of blood-vessels, and that when repeated injections are made, the rise in pressure diminishes with each injection until a fall in pressure occurs. This change in the effect of repeatedly administered injections of pituitary extracts is designated as its "depressor action." No attempt will be made here to cover with detailed references the previous work on this subject, which is readily accessible in a recent article by Wiggers.[1]

A brief summary of the commonly accepted interpretation of these results seems, however, necessary. In 1899 Schäfer and Vincent[2] suggested that extracts of the pituitary gland contained two substances, one having a pressor, the other a depressor effect, the former inducing a constriction of arterioles, the latter a dilatation. After repeated injections of the extract of pituitary gland, the pressor substance lost and the depressor retained its influence on the blood-vessels, so that the rise in pressure was gradually replaced by a fall. A perusal of the work of Schäfer and his co-workers emphasizes the fact, however, that this must be regarded as a plausible explanation rather than, as is commonly assumed, a demonstrated fact, for they not only failed to isolate these substances chemically,[3] but they have not excluded the following possibilities of error, namely, (1) the decreased cardiac output may be accountable for the fall of blood-pressure; (2) an increased central dilator action develops, overpowering the peripheral constriction; (3) lack of proof that the peripheral vessels dilated when the fall of pressure occurs; (4) repeated injections can convert the constriction of peripheral origin into a dilation.

The scope of this research was limited to the solution of some of these undetermined problems by more direct experimental methods, and

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1. Wiggers: Jour. Med. Sc., 1911, cxli, No. 4, p. 502.

2. Schäfer and Vincent: Jour. Phys., 1899, xxiv, 19; Jour. Phys., 1900, xxv, 87.

3. Schäfer and Herring: Phil. Tr., Roy. Soc. London, series B, 1908, cxcix, 1.

other facts regarding this drug's action were touched on only as necessity demanded. By this means, it was hoped to throw additional light on the nature of the depressor action of pituitary extracts.

II. MATERIAL AND METHODS USED

The infundibular portion of the gland was ground up and dried without any preservative. A solution of this material in Locke's solution was made of such strength, that each c.c. of the solution equaled 0.1 gm. of fresh gland. This was then heated on a steam bath, so as to precipitate partly the protein material, which was later separated by filtering. The solution had a specific gravity of 1.010. This preparation deteriorated on standing. When the solution was sterilized, it kept permanently. This preparation which was made each day was used as a standard of all the work, and is the one referred to throughout the paper unless special designation is made. At times, however, a solution made in the same way, but of greater strength, was used. Pituitrin, the preparation which has been described by Aldrich, was also employed.[4]

For these experiments both dogs and rabbits were used, but principally the former. The anesthetic was uniformly chloretone (0.3 gm. per kilo of body weight) in oil, injected intraperitoneally. In dogs a subcutaneous injection of morphin preceded the administration of chloretone. The external jugular vein was exposed for injections. The blood-pressure was recorded through the carotid artery, by means of mercury or Hürthle's manometers. The contractions of the dog's heart were recorded by means of the cardiac oncometer. The cardiograph was used in case of the rabbit. In all experiments on dogs the breathing was natural. After the insertion of the oncometer the chest was sewed up, stitches being taken through the cut intercostals, through the muscles of the chest and through the skin. The site of the incision was covered with a mixture of petrolatum and wax, which rendered the thorax air-tight. The respirations were recorded by the transmission of the changes in intrathoracic pressure through a thoracic cannula. During the period in which the chest was open, artificial respiration was given in the manner common to laboratories.

III. THE EFFECT OF BLOOD-PRESSURE

The blood-pressure phenomena arising from the intravenous injection of extracts of the pituitary gland into anesthetized animals are in no wise peculiar to this particular work, but correspond to the results reported generally. The results from the initial injection, allowing for normal variations, are constant and the tracings typical. Within a few seconds of the injection, the blood-pressure rises abruptly and

4. Aldrich: Am. Jour. Phys., Proc. Soc., 1908, xxi, 23.

sharply, the cardiac oscillation increases in size, and the heart-rate is slowed. A tracing presenting these results may be designated as a "typical pituitary curve." However, a number of variations are observed such as instances (1) in which no slowing up occurs, (2) in which, as the summit of the pressure height is neared, a slight and often imperceptible fall in pressure takes place (this fall in pressure is very transient, and the increase in pressure is soon resumed and generally reaches a point above that prior to the fall), or (3) in which, after a gradual fall a second slight increase in pressure occurs (Fig. 1). The second and third variations occur very frequently in rabbits but only to a limited extent in dogs.

The rise of pressure persists for a considerable time, but generally approaches normal again within ten minutes, and only in exceptional cases remains above normal for a period of twenty minutes. The first "repeat dose" in dogs is not inactive, as has been shown by Schäfer, for other animals. In none of these experiments did a second injection fail to produce a sharp rise in pressure. In rabbits, however, a large number of second injections were ineffective or caused a fall in pressure. In dogs the rise following the second injection is much more gradual, and the extent and duration of the rise is not so pronounced as after the first injection. This progressive lessening and lagging in the rise in pressure may be obtained for four or five injections, after which time the substance fails to act or else causes a depressor effect (Fig. 2).

All further experiments were instituted in an attempt to explain these blood-pressure variations.

IV. ACTION ON THE BLOOD-VESSELS

Peripheral Action.—Since the rise in pressure is mainly attributed to a peripheral action on the blood-vessels, an insight into the exact nature and extent of this action was attempted by the perfusion method. The individual organs were isolated and perfused with a regularly interrupted stream of Locke's solution under constant pressure, and heated by passage through a condensing tube. The outflow was constantly recorded, together with the oscillation of the perfusion pressure. The preparation of pituitary extract, already described, was slowly injected into the circulating medium with a hypodermic syringe.

Kidney.—Ninety-five injections were made. Of these, eighty-five gave an initial constriction of the blood-vessels, while ten injections were followed by a dilation. In sixty-five a single vaso-constriction with a quick return to normal occurred. In the remaining thirty a secondary action of various kinds was observed. Five injections gave a constriction of the blood-vessels followed by a subsequent dilatation; five injections constricted the renal vessels permanently; ten of the injections causing

a primary constriction of the blood-vessels were followed by a secondary constriction; of the injections producing an initial dilatation, seven showed a secondary constriction. In ninety-two of the total ninety-five experiments (97 per cent.) a constriction took place, and in only three (3 per cent.) was there a pure dilatation.

Repeated injections gave no evidence of fatigue on the part of the vessels. As high as twenty injections were made on a single kidney, and the response to the drug was as prompt in the last as in the first. After the fifth or sixth injection, the amount of constriction was no longer constant owing to the edema of the organ. Up to this point, however, injections of equal quantities of pituitary extract gave the same amount of constriction (within 2 per cent.). Since this is true, it is possible that herein lies a reliable method for the standardization of the preparations of this drug. When a series of injections were made with doses ranging from 0.3 c.c. up to 2 c.c., the amount of constriction was not proportional to the amount of the substance injected. For example, the constriction that followed an injection of 2 c.c. was not double that which followed an injection of 1 c.c.

Spleen.—The numerous collateral vessels to this organ were tied off. The capsule was not removed as in the case of the kidneys. A series of ten spleens were perfused. Following an introduction of 2 c.c. of pituitary extract the splenic vessels showed a constriction with an average decrease in outflow up to 60 per cent. and a duration of the constriction of about two minutes.

Liver.—The livers of guinea-pigs were perfused through the portal vein. Pituitary extract caused a constriction of the hepatic vessels which was not so marked as was obtained with renal vessels but which persisted for a greater length of time.

Coronary Vessels.—For perfusing the heart, Ringer's solution was used. The cannula was placed in the descending branch of the left coronary artery, the heart being in standstill. The transverse branch of the left coronary artery and the right coronary were tied off. When dogs' hearts were perfused by this method, the injection of the pituitary extract was always followed by a constriction of the coronary vessels. Coronary vessels which responded readily to both adrenalin and pituitrin were injected with ergotoxin, which paralyzes the nerve endings or myoneural junctions. Subsequent injections with adrenalin elicited no constriction, and in some cases even a dilatation occurred, while the constrictor action of the pituitrin was even more pronounced than before the injection of ergotoxin. It would appear that adrenalin and pituitary extract have not a common point of action, and that the muscle fiber itself is the point of action for the latter.

Lungs.—Solitary lobes of the lung of guinea-pigs were perfused. The lobe was inflated through the bronchus and tied off, so that the inflation was maintained throughout the experiment. Unless this was resorted to, the changes in the vessel wall were not apparent, since the air spaces would permit alterations to take place in the vessels which would not affect the recording apparatus. After this precaution had been taken, it could be seen that the injection of pituitary extract produced a constriction of the blood-vessels.

Embryonic Vessels.—The bodies of unborn pups were perfused through the thoracic aorta. The thoracic veins were cut to allow an easy outflow for the perfusing fluid. Both adrenalin and pituitrin were

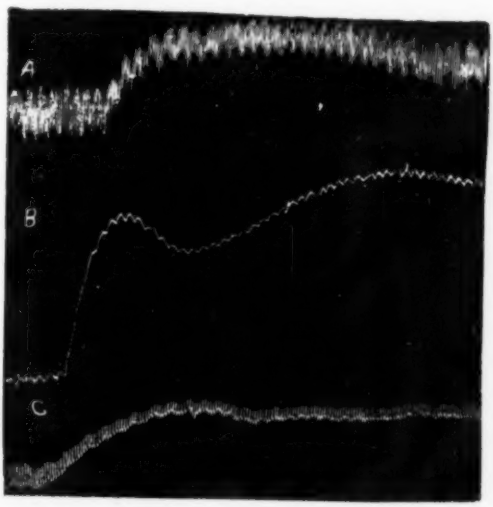

Fig. 1.—A, blood-pressure tracing showing typical effect of pituitary extract. B and C, variation types.

injected, and the response from each consisted in a marked constriction of the blood-vessels.

Limbs.—In one experiment the lower limb of a living and intact animal was perfused through the femoral artery. The sciatic nerve was dissected and the thigh, exclusive of this nerve, was tied off with a bandage from the other parts of the body. A constriction, such as had been seen in the other experiments, took place here on the injection of pituitrin.

Summary.—These experiments show that the pituitary extract acts on all the vessels of the body, and that the action is similar in quality for all parts of the body, though the intensity and duration of the action

varies slightly in different organs. There is no indication that the peripheral mechanism becomes fatigued on repeated administration of the substance, for with repeated administration there may be repeated constriction of the blood-vessels.

Central Nervous Action.—Since perfusion experiments failed to show any change in reaction of the peripheral vessels in any organ after repeated injections, it seemed that the fall in pressure must be due to a central action. Sollmann and Pilcher,[5] in their experiments on the central nervous action of drugs, have shown that pituitary extract

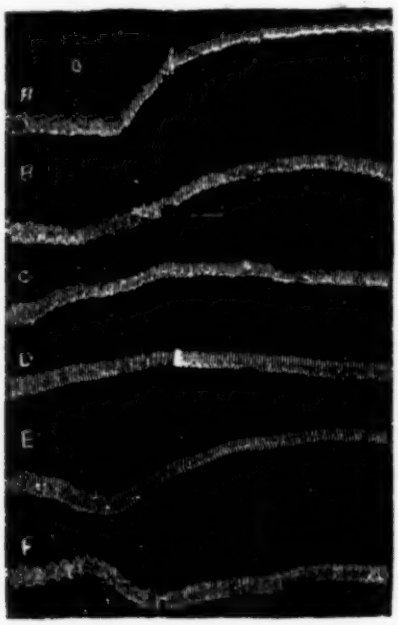

Fig. 2.—Effect of consecutive injections of equal amounts of pituitary extract on blood-pressure of rabbit.

may cause a dilatation of the splenic vessels by reason of an action on the nervous system. By the use of a similar method, it was hoped to determine whether the fall in blood-pressure after repeated injections of pituitary extract was due to an increase of this dilator action of the central nervous system or to a diminution of the peripheral constrictor action. In this work, dogs not exceeding 12 kilos were used. Artificial respiration was given during the first part of the experiment. The

5. Sollmann and Pilcher: Jour. Pharmacol. Exp. Therap., 1910, i, 571.

thorax was opened and the heart was placed in an oncometer, after which the thorax was closed and the volume changes of the heart recorded during natural respiration. The carotid was exposed for recording the blood-pressure. The kidney was brought to the surface through as small an opening as possible. The fatty mass around it was carefully removed and the vein and artery were exposed, care being taken to preserve from injury the nerves running along the vessels. The renal artery was clamped off near the aorta and cut. A cannula was inserted into the renal end. The vein was then ligated and cut peripherally to the ligature. The fibrous capsule of the kidney was partially removed. The kidney, which was connected with the body only through the nerve supply, was then perfused with a rhythmical stream of Locke's solution and the oscillations recorded by a Hürthle manometer.[6] Pituitary extract

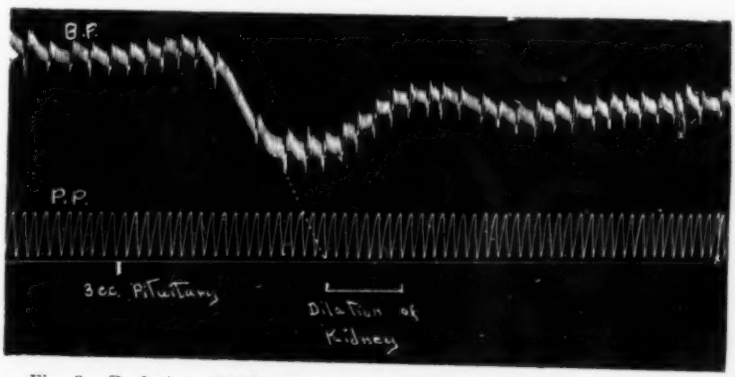

Fig. 3.—Perfusion of kidney with nerve supply intact. B. P, carotid blood-pressure; P. P., perfusion pressure (after repeated injection of extract).

was now injected into the jugular vein. At the time the carotid pressure was highest, the diastolic perfusion pressure supplying the kidney fell slightly, indicating that a dilatation of the renal vessels had taken place through an effect on the vasomotor center. The perfusion was then discontinued to prevent the marked edema which occurs when the capsule is not removed. Repeated injections of pituitary extract were then given, until the animal reacted by a fall in pressure, as was shown by the carotid tracing. The perfusion was then resumed. On a further injection of the pituitary extract into the jugular vein, a dilatation of the vessels and a fall in carotid pressure took place, and at the same time a dilatation occurred in the vessels of the perfused kidney (Fig. 3). This dilatation, however, was not increased over that which occurred with

6. Wiggers: Am. Jour. Phys., 1907, xx, 209.

the rise in blood-pressure during the first part of this experiment; this fact would indicate that the fall in blood-pressure is not due to an increase of the dilator action of the central nervous system. This is further substantiated by the fact that the dilatation of the renal vessels comes on after the maximum fall in blood-pressure has been reached, and, in this case, the carotid pressure shows no indication of having been influenced by the nervous system (Fig. 3).

V. THE EFFECT ON THE HEART

Since it appears that the subsequent fall of blood-pressure after repeated injections of pituitary extracts is not due to a fatigue of the peripheral vessels, nor to a heightened influence of the dilator effect of the central nervous system, the influence exerted by the heart on the blood-pressure was next determined.

The conclusions as to the influence of pituitary extract on the heart were based on the results obtained from 249 injections into the living animal (dogs, rabbits) and from the perfusion of eighteen rabbits' hearts.

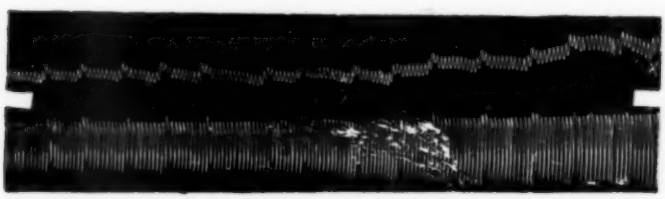

Fig. 4.—Effect of pituitary extract. Rise in blood-pressure (below) accompanied by a gradual depression of the heart. (Reduced to two-thirds original size.)

In considering the effect on the amplitude of the heart's contraction, only those experiments were utilized in which actual cardiac tracings were obtained. Changes in the oscillations of the blood-pressure, which have been interpreted by some investigators on this subject as characteristic of changes in the heart's action, were not accepted as such by us.

Perfusion Experiments.—Locke's solution was used for the perfusion of the heart. The ventricular pressure was recorded by means of a cannula pushed through the semilunar valves of the pulmonary orifice, down into the right ventricle, this cannula being connected with a tambour. The auricular pressure was recorded in a similar way through the inferior vena cava. The perfusion fluid passed out through the superior vena cava; a cannula was placed in this vessel and was elevated to that height which would give a hydrostatic pressure proper to insure the recording of the auricular changes through the inferior vena cava. The effects attending these experiments on the amplitude and rate of the heart-beat may be summarized as follows:

Amplitude: Ninety-four per cent. of injections caused a decrease in amplitude; 6 per cent. of injections caused no change in amplitude; one experiment gave an increase in amplitude.

Rate: Seventy-five per cent. of the hearts were slowed; 25 per cent. of the hearts were not affected; at no time was the rate increased.

In the living animal neither the rate nor the amplitude of the heart-beat shows the constancy that is found in the perfused hearts. The heart is affected by the pituitary extract through several avenues. A vagus influence is exerted and there is a direct action on the heart muscle as well. These two factors, with combinations of the two, create a complex set of variations in rate and amplitude. The scope of this paper does not permit of the discussion of these variations of the heart's action *per se*, but only as they affect the blood-pressure. For the present purpose it is sufficient to say that in the greatest number of these experiments the heart's rate was moderately slowed early in the drug's action and remained so throughout the experiment. The remaining small per-

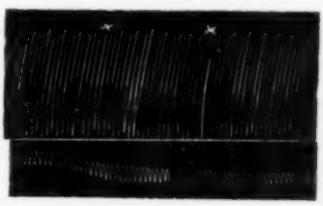

Fig. 5.—Cardiograph tracing (above) showing a strengthening of the heart, with a fall in carotid pressure (below).

centage of experiments is made up of the total of cases in which the rate was not affected, cases in which the rate was increased, and cases in which the rate was increased early but later gave way to a slowing. Similarly, the amplitude of the heart's action after the administration of pituitary extract showed an early gradual depression which was typical. The chief variations were a strengthening action occurring early and a strengthening action occurring late. These various actions on the heart are responsible for the following definite changes in the shape of the blood-pressure tracing:

1. When the amplitude and rate of the heart are gradually decreased from the start, as in typical experiments, the changed cardiac output is not shown in the blood-pressure tracing, except that the rise of the curve as a whole is less pronounced (Figs. 1 and 4).

2. Where the myograph tracing shows a marked and sudden depression of the heart, due to the action of pituitary extract, the blood-pressure shows a notch, occurring as the summit of the pressure height

is reached, varying in size and extent in proportion to the extent and duration of the heart's depression. (Fig. 1 *B*.)

3. When the heart is strengthened during the early action of the drug, no notch is seen in the blood-pressure curve, and there is no indication of the heart's action.

4. The strengthening of the heart which occasionally occurs late in the drug's action, coming on after the height of the blood-pressure curve has been passed and a fall is taking place, shows on the downward limb of the blood-pressure tracing as a transient and very temporary increase in pressure. (Fig. 1 *C*.)

5. Cases sometimes occur in which an early cardiac depression causes first a notch or hump in the blood-pressure curve, while a later strengthening of the heart's action produces a second notch and hump. Careful

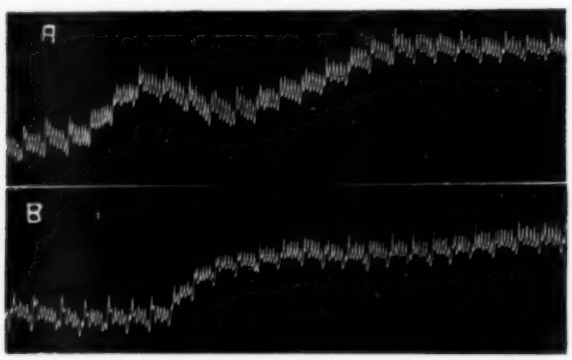

Fig. 6.—A, effect of 2 c.c. of pituitary extract mixed with 50 c.c. of blood drawn from the animal. B, effect of 2 c.c. alone.

scrutiny of the curves indicates, however, that these depressions in the blood-pressure are not the same either in conformation or in time as those obtained after repeated doses of pituitary extract. (Compare Fig. 2 *F* with 1 *B* and 1 *C*.)

It has been suggested by Wiggers[1] that the depressor action of pituitary extract might be due to an increased weakening of the heart. This suggestion has not been borne out by this work. In the first place, the weakening of the heart, as has been seen already, is not constant, and the fall in blood-pressure may occur even when the heart is strengthened (Fig. 5). In the second place, the depression in the action of the heart is not greater than with the first injection. Third, the time relations between the depression of the heart's action and the beginning of

the fall in pressure are not synchronous. These facts taken together exclude the possibility of attributing the real fall in pressure which is typical of repeated injections to the cardiac depression.

VI. THE BLOOD

Blood-pressure tracings, illustrating the effect of repeated injections of pituitary extract, show a gradation from the sharp, abrupt rise in pressure following the first injection, through a number in which the rise in pressure gradually becomes less marked and less abrupt, until the tracings are reached in which an actual fall of pressure is observed. So uniform and constant are these gradations, as the blood becomes more saturated with the substance, that a change in the drug brought about by the action of the blood itself was looked on as the last possible cause for its diminished activity and the fall in pressure. To test this possibility, however, several experiments were performed.

EXPERIMENT 1.—Sixty c.c. of blood were drawn from the femoral artery of a dog. This blood was defibrinated and filtered. Two c.c. of pituitrin were mixed with the blood, and the mixture was allowed to stand for from twelve to fifteen minutes. The blood and pituitrin were then injected into the animal through the jugular vein, the blood-pressure being recorded from the carotid artery. There occurred in every case a fall in pressure, followed by a rise (Fig. 6). Both the fall and the rise in pressure due to the drug were somewhat masked by the rise in pressure due to the increased volume of blood. This action took place when the blood-pituitrin injection was given, but was much more pronounced if an injection of pituitrin alone was given previously. As a control, an equal quantity of pituitrin in an amount of salt solution equalling that of the blood was injected after the injection of the blood-pituitrin. The result was a sustained rise in blood-pressure.

EXPERIMENT 2.—The femoral artery was exposed and a cannula placed in its ramaprofunda. A bandage was placed loosely around the thigh as high up as possible. The femoral artery was then clamped off above, and 2 c.c. of pituitrin were injected into the ramaprofunda. The femoral artery was released and the bandage drawn tight, so that the return of blood to the rest of the body was cut off. In this way, the extract was mixed with arterial blood and distributed to the greater part of the limb. At the end of from ten to fifteen minutes the bandage was cut and the blood allowed to flow into the general circulation. A fall in pressure occurred, together with a slowing of the heart. When a limb was similarly bandaged, but without pituitrin injection, there was no change in pressure when the bandage was released.

EXPERIMENT 3.—A limited number of experiments were carried out in which the kidneys were perfused with blood. Pituitrin was injected into the living animal until the blood-pressure fell. The blood was drawn and defibrinated. A mixture of two parts of blood to one part of salt solution was used both as perfusing medium and as the solvent for the pituitary extract. In this way the specific gravity and viscosity of the perfusing medium and of the material injected into the medium were the same, thus excluding any change which might be attributed to altered viscosity. Kidneys thus perfused showed a dilation of the blood-vessels when pituitary extract was injected.

Since this work has been completed, Cushing and Goetsch,[7] working with the cerebral fluid from patients with tumor of the hypophyseal

7. Cushing and Goetsch: Am. Jour. Phys., 1910, xxvii, 60.

region, have obtained blood-pressure curves following injections of this cerebral fluid, which they believed to contain the secretion of the pituitary gland. These tracings are very similar to the tracings obtained by us in experiments above, series one and two.

From these experiments it seems clear that whenever the pituitary extract is present in the blood or lymph in sufficient concentration, the usual action of the extract is reversed so that the substance causes a dilatation of the vessels and a fall in the pressure.

CONCLUSIONS

1. The depressor action of pituitary extract elicited by repeated injections is not due to the fatigue of any peripheral mechanism, nervous or muscular. Perfusion experiments indicate that it constricts all the blood-vessels of the body by a direct action on the muscles of the arterioles, and often repeated injections show practically no decrease in the constrictor reaction.

Organs removed from animals giving only a depressor reaction with pituitary extract show on perfusion with the extract in Locke's solution the typical constriction of their vessels.

2. The depression of blood-pressure following numerous injections of pituitary extract is not due to an overbalancing of peripheral constriction by a central dilator influence. Such a counteracting dilator influence of central origin is always weak and no more pronounced after repeated than after the initial reaction, and moreover it does not come on until the fall of pressure is at its lowest.

3. Sudden depression or slowing of the heart, though occasionally showing as a notch in the blood-pressure records, is not the cause of the typical drop in pressure obtained after repeated injections, for such depression is not similar either in conformation or in time to the depression obtained by the latter means, and may in fact exceptionally occur with a strengthened heart.

4. Experiments indicate that when the blood becomes sufficiently saturated with pituitary extract, an interaction takes place which converts its constricting action on the peripheral vessels into a dilating one.

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OBSERVATIONS ON THE HEMOLYTIC SKIN TEST FOR CANCER*

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In February, 1910, appeared an article by Elsberg, Neuhof and Geist[1] describing a skin reaction in carcinoma from the subcutaneous injection of human red blood-cells. The results which they obtained were so remarkable that, were they correct, we should have probably the most valuable test yet discovered for the diagnosis of carcinoma. The test, in brief, consists in the subcutaneous injection of 5 minims of a 20 per cent. suspension of washed human red cells into the flexor surface of the forearm of the individual suspected of having cancer. A positive reaction consisted in the appearance within six hours of a "somewhat irregular oval area with a well-defined margin measuring from 1 by 2 cm. to 3 by 5 cm. The margin is often surrounded by a whitish areola. The color of the lesion varies from a brownish-red to a maroon with, rarely, a bluish tinge. The lesion is distinctly raised from the surrounding skin surface. At times this elevation is so slight that careful examination in good daylight is necessary to recognize it. . . . When the lesion has disappeared, there remains behind a flat yellowish or greenish discoloration such as is left by any small ecchymosis."

Up to the time of publication they had made 684 injections on 432 patients with the following summarized results: A positive reaction was found in 90 per cent. of patients with carcinoma (excepting the very advanced). No reaction was observed in 94 per cent. of patients suffering from other diseases. A reaction of this nature would undoubtedly be of inestimable value in the diagnosis of obscure cases where cancer was suspected.

The source of the corpuscle suspension was described in detail and hedged about with numerous restrictions. "Tuberculosis and syphilis must be excluded; the patient must not only be free from any evidence of disease, but must not have been recently ill, nor have received any injury, must not have had even the slightest operation, and must not have recently had an anesthetic. . . . The blood can, however, be taken from a patient during the early stages of ether anesthesia." They obtained their blood from children in hospital who were to be operated on for hernia.

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1. Elsberg, Neuhof and Geist: Am. Jour. Med. Sc., 1910, cxxxix, 264.

It was a very interesting suggestion of Elsberg that hemolysis of human red blood-cells be tried not on serum of cancer patients but *in vivo*, the foreign red cells there being bathed in plasma so that any amount, however small, would be brought to the part and produce the hemolysis. The suggestion would undoubtedly have proved of great value, had it been founded on actual, accurate results with hemolysis *in vitro*. I shall examine the evidence now accumulated in regard to the specificity of the hemolysis of human red blood-cells by serum of cancer patients, and then I shall briefly relate the results of personal experiments.

I. GENERAL REVIEW OF HEMOLYTIC EXPERIMENTS

Engel,[2] and later Mertens,[3] could not prove the existence of specific antibodies (*Krebssubstanzen*) in the serums of cancer patients. Fischel[4] found that in about one-half of cases of malignant tumors, the serum had an increased hemolytic power compared with serum from normal persons. He worked with human serums and red cells of chickens. He showed similar hemolytic power in serums from cases of diabetes, pernicious anemia, chronic endocarditis and tuberculosis. Weil,[5] using human red blood-cells, found results absolutely in accord with those of Fischel. The reaction is not specific for tumors (cancers).

Crile,[6] however, was led to test the blood serum of cancer patients against suspensions of normal human red cells, although it was known that there was no specific hemolytic reaction. His results were most astounding. For example, up to 1908 he had studied 591 cases. Of these, 211 serums of normal individuals showed no hemolysis. In 153 cases of cancer there were 85 per cent. positive hemolytic serums. But in 92 per cent. of cases of tuberculosis there was reversed hemolysis, i. e., normal serum hemolyzed the corpuscles of the tuberculous patients. This work of Crile has not been confirmed; on the contrary, no one has been able to obtain such constant results in hemolysis.

R. Weil[7] states that human serum in various diseases is occasionally hemolytic toward the corpuscles of other human individuals. He found that extracts of lymphosarcoma of dogs were not hemolytic for dogs' corpuscles, but necrotic tumors possessed a high hemolytic power. He further showed that in some dogs with necrotic tumors, the serums were hemolytic in some degree for all dog red corpuscles. Normal dog serum is rarely hemolytic.

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2. Engel, C. S.: Deutsch. med. Wchnschr., 1903, xxix, 897.
3. Mertens, V. E.: Deutsch. med. Wchnschr., 1904, xxx, 203.
4. Fischel, W.: Berl. klin. Wchnschr., 1908, p. 882.
5. Weil, R.: Jour. Am. Med. Assn., 1908, li, 158.
6. Crile: Jour. Am. Med. Assn., 1908, li, 2036.
7. Weil, R.: Jour. Med. Research, 1908, xix, 281.

Ottenberg and Epstein[8] performed many tests with serums of patients on washed red corpuscles of other patients, in an attempt to test the value of the hemolytic reaction in cases of cancer. Their experiments were performed in groups, every serum being tried in turn on the washed red cells of every other number of the group. While they found that the serums of subjects with malignant tumors were hemolytic in 76 per cent., in all other diseases tried the serums were hemolytic in 50 per cent. They say, "as a result of this work, the chief object of which has been to determine the value of isohemolytic reactions in diagnosis, we are forced to the unsatisfactory conclusion that the method is not at present to be relied on for diagnosis."

In a further attempt to show the presence of hemolysins in body fluids, R. Weil[9] tested the lytic reactions of ascitic fluids from cases of spontaneously cured cancer (Hodenpyl's case), from other cases of long standing, apparently quiescent, cancers and fluids of transudates. He used the red cells of fifty-three persons of whom twelve had cancer. "All of the fluids occasionally manifested hemolytic properties, and, in the case of some, this was more general than in others. It was not, however, possible to distinguish the cancerous fluids in any way by their mode of reaction, despite the fact that the blood serum of cancerous individuals has, in general, been found by previous workers to possess more marked hemolytic properties than the normal."

The general conclusions reached by all investigators except Crile is that there is nothing specific in the hemolysis of normal human red cells by the serums or cancerous fluids of patients suffering from cancer. Such a reaction is not available as a means of diagnosing cancer, although serums of patients with necrotic tumors (cancers) do seem to have a marked hemolytic power on normal red cells.

II. PERSONAL OBSERVATIONS

The results of the observations made on seventy-four patients suffering from a variety of diseases, including carcinoma, are graphically shown in the tables. The last table is a summary of the work. The blood was taken from perfectly healthy young adults, washed in several changes of normal salt solution and made up to the desired percentage suspension.

It seemed possible that several factors might influence the reaction *in vivo:* (1) The volume of injected suspension; (2) the concentration of the suspension; and (3) the relation of the subcutaneous tissue to the skin, that is, whether the skin was loosely or tightly adherent to the subcutaneous tissues. Several injections of red cells hemolyzed with distilled water were made in order to see what appearance would result, as it

8. Ottenberg and Epstein: THE ARCHIVES INT. MED., 1909, iii, 467.
9. Weil, R.: Jour. Med. Research, 1910, xxiii, 85.

TABLE 1.—OBSERVATION 1.—SIXTEEN CASES

Blood from white, healthy male, 21 years old, one month after uncomplicated operation for strangulated hernia. Site of injection, forearm flexor surface; amount 5 minims, 20 per cent. suspension. Time 2 p. m.

No.	Hosp. No.	Diagnosis.	Appearance After Six Hours.	Appearance After Twenty-Four Hours
1	7615	Mitral stenosis	Pinkish, slightly raised oval area, 2x5 cm.	Purplish discoloration of spot.
2	7834	Arteriosclerosis	Absolutely no evidence.	Same.
3	7822	Otitis media	Absolutely no evidence.	Same.
4	7809	Rheumatic fever	No evidence.	Very slightly raised oval pink area, 1.5x4.5 cm.
5	7530	Tuberculous hip	Slightly raised pink oval spot, 2x3 cm.	Slight bluish discoloration considerably raised and firm.
6	7688	Rheumatic fever	No evidence.	Same.
7	7832	Lead colic	Slightly pink raised oval spot, 1.5x3 cm.	Purplish discoloration, raised slightly, 4x6 cm.
8	7663	Carcinoma stomach	No evidence.	Spot 3x5 cm. like bruise, not raised. May have been early reaction.
9	7826	Sarcoma shoulder	Slight discoloration pinkish, 2x3 cm.	"Black and blue" spot, flat, 3x4 cm.
10	7780	Tuberculous hip	No evidence.	"Black and blue" level spot like Case 8.
11	7768	Gunshot wound, arm	No evidence.	Same.
12	7806	Secondary cancer, liver	No evidence.	Same.
13	7583	Typhoid convalescent	Very positive. Bright pink oval raised, 2x5 cm. No pain.	Oval "black and blue" spot, 4x6 cm.
14	7562	Carcinoma stomach, cachectic.	No evidence.	No evidence.
15	7746	Carcinoma stomach (?)	Oval, pinkish, slightly raised, 1x2 cm.	Slight discoloration, purplish green, 3x1.5 cm.
16	7640	Typhoid convalescent	Oval, bright pink, 1.5x3.5 cm. Slightly raised.	Slight "black and blue" spot.

TABLE 2.—OBSERVATION 2.—NINETEEN CASES

Blood from same man, 4 days old, no laking seen. Site of injection, forearm. Amount injected 5 minims. Time 11 a. m.

No.	Hosp. No.	Diagnosis.	Appearance After Six Hours.	Appearance After Twenty-Four Hours.
1	7701	Tabes dorsalis	Slightly raised, not discolored	Flat pink spot, 3x5 cm.
2	7812	Tabes dorsalis (?)	No evidence	Very faint, slightly greenish brown spot.
3	7427	Arthritis deformans	No evidence	No evidence.
4	7745	Syphilitic ulcer, leg	Very slight brown discoloration, very slightly raised.	Slight brownish discoloration.
5	7681	Gonorrheal rheumatism	No evidence	Only very faint brown spot, 2x3 cm.
6	7795	Chancroids	No evidence	As above.
7	7831	Tertiary syphilis	Very slight greenish-brown discoloration, slightly raised.	Flat slight greenish spot, 2x4 cm.
8	7630	Syphilitic ulcer, leg	No evidence	Slight reddish spot, 2x3 cm.
9	7788	Gonorrheal rheumatism	No evidence	Small "black-and-blue" spot.
10	7786	Gonorrheal rheumatism	Slight brownish discoloration, 3x1.5 cm., slightly raised.	Brownish green spot.
11	7759	Myocarditis	Nothing	Nothing.
12	7474	Blastomycosis	Dirty brownish discolored area	Greenish spot, 2x4 cm.
13	7718	Traumatic myelitis	No change of color, slightly raised	Very slight pink, 2x4 cm.
14	3521	Spastic paraplegia	Nothing	Slight pinkish-purple spot, slightly raised, somewhat tender.
15	29	Tabes	Purplish-red discoloration, 1x5 cm., slightly raised.	Nothing seen.
16	7132	Spastic paraplegia	Very slight lilac spot, slightly raised, 2x4 cm.	Very tender, large pinkish area, slightly raised.
17	7529	Multiple sclerosis	Slightly sensitive, slightly raised, no color	Slightly tender and raised, light pink color.
18	2020	Traumatic myelitis	The faintest pink color, very slightly raised	Same. Slightly tender.
19	7667	Gout	Raised, soft, slightly mottled, irregular oval area, tender.	Same.

TABLE 3.—OBSERVATION 3.—SIX CASES

Blood from athletic white man, well for years, aged 25. Five injections of blood suspension; (a) two into left forearm; (b) two into right forearm; (c) one, skin over biceps;* (a) 5 and 10 minims of 20 per cent. suspension; (b) 5 and 10 minims of 10 per cent. suspension; (c) 5 minims 20 per cent. laked in distilled water; injected 11 a. m., examined 5 p. m.

No.	Hosp. No.	Diagnosis	a 5	a 10	b 5	b 10	Remarks
1	7637	Carcinoma stomach	0	0	0	0	Irregular brownish red spot.
2	7679	Tuberculous hip	0	Slight	0	0	Irregular brownish red spot, 3x5 cm.
3	7619	Fracture foot	0	++	0	0	Brownish red bruised spot.
4	7863	Sprained ankle	0	+	0	0	As above.
5	7856	Lumbago	0	0	0	+	As above.
6	7602	Ulcer leg	0	+	0	0	As above.

* All areas showed dark bluish-black discoloration after six hours.
++ denotes considerable discoloration of black-and-blue appearance.
+ denotes very slight discoloration of black-and-blue appearance.

TABLE 4.—OBSERVATION 4.—SIX CASES

Blood from healthy white female, well for years, aged 22. Four injections of corpuscle suspension, (a) two into left forearm, (b) two into right forearm; (a) 5 and 10 minims 20 per cent. suspension; (b) 5 and 10 minims 40 per cent. suspension; injected 11 a. m., examined after six and twenty-four hours.

Number	Hospital No.	Diagnosis	a 5		a 10		b 5		b 10		Remarks
			6 hours	24 hours	6 hours	24 hours	6 hours	24 hours	6 hours	24 hours	
1	7835	Rheumatic fever	—	+	—	+	—	+	—	+	+ is very slightly brownish-green color.
2	7846	Rheumatic fever	—	+	—	+	—	+	—	+	+ is faint slight greenish color.
3	7851	Rheumatic fever	+	+	+	+	++	++	++	++	All showed large, distinct greenish-brown flat spots, fading off into normal skin.
4	6674	Arthritis deformans	+	+	—	+	+	+	—	+	Five minims given near wrist, where skin is rather tight. All showed only small, not very distinct brown.
5	7575	Aortic insufficiency	—	+	—	++	+	++	++	++	Right arm showed colored spots, left arm nothing;
6	7842	Stricture small intestine (tuberculous).....	—	+	+	++	—	+	+	++	all after twenty-four hours showed discoloration. Ten minims more distinct than 5 minims.

TABLE 5.—OBSERVATION 5—SIX CASES

Blood from healthy male, aged 26, taken March 25, 1910, used March 28, 1910. Four injections. Two of 20 per cent. suspension, 5 m. left forearm near elbow, 10 m. near wrist; two of 40 per cent. suspension, 5 m. right forearm near elbow, 10 m. near wrist. Injected 10:30 a. m. Examined after six and twenty-four hours.

No.	Hosp. No.	Diagnosis.	Appearance After Six Hours.	Appearance After Twenty-Four Hours.
1	7902	Influenza	Marked, 4x5 cm., bright reddish green spot lower right. *Very* slight greenish upper. Lower left not so marked. Upper left very slight, but more distinct than upper right.	All spots brownish blue, rather dark, very distinct; lower right more marked.
2	7823	Pneumonia, delayed resolution.	Distinct discoloration lower right, less upper. Slightly seen on lower left. Nothing upper left.	All slightly greenish and alike.
3	7796	Typhoid convalescent.....	Nothing seen at any spot.....	All slightly pale green, left trifle more.
4	7801	Typhoid convalescent.....	Nothing seen at any spot.....	Only right upper one shows slight green color.
5	7784	Typhoid convalescent.....	Only on upper right arm very slight pink area, others nothing.	All show pale, light green, diffuse stain, right more than left.
6	7802	Typhoid convalescent.....	Nothing seen at any spot.....	All show slightly pale green diffuse stain.

TABLE 6.—OBSERVATION 6.—EIGHT CASES

Blood from healthy white female, aged 23. Site of injection, upper left arm over biceps. Amount 10 minims. Suspension 20 per cent. corpuscles. Time 10:30 a. m., April 1, 1910. Examined after six and twenty-four hours.

No.	Hosp. No.	Diagnosis.	Appearance After Six Hours.	Appearance After Twenty-Four Hours.
1	7842	Tuberculous stricture intestine.	Raised purplish brown, slightly painful, 3x5 cm.	Black and blue, slightly raised.
2	7746	Cirrhosis liver	Considerably raised. Color, size as above. Painful.	Large, hot, swollen, tense area, painful, brownish purple.
3	7640	Typhoid convalescent	Raised, purplish-brown spot, slightly tender, 2x3 cm.	Black-and-blue flat, 3x5 cm.
4	7694	Tuberculous hip	Slight brownish spot, slightly tender	Slight greenish spot, flat, no tenderness, 2x3 cm.
5	4346	Chronic tuberculous osteomyelitis.	Brownish purple flat spot, 3x5 cm. No tenderness.	Black-and-blue spot, flat, no tenderness.
6	7826	Sarcoma (low)	Nothing seen; only slightly raised, slight tenderness.	Slight greenish spot, slight tenderness, 2x3 cm.
7	7529	Fracture patella	Very slight brownish pink, slightly raised spot, 3x5 cm.	Large, 8x6, purplish-red, raised area. Slight tenderness.
8	7618	Fistula in ano	Slight soreness. Otherwise nothing	Slight pink spot, 1x3 cm. Slight tenderness.

TABLE 7.—OBSERVATION 7.—THIRTEEN CASES

Blood from same person as Observation 6. Site, right forearm. Amount 10 minims. Suspension 20 per cent. corpuscles. Time 11 a. m., April 8, 1910. Examined after six and twenty-four hours.

No.	Hosp. No.	Diagnosis.	Six Hours.	Twenty-Four Hours.
1	7907	Gout and tuberculosis	Nothing	Nothing.
2	7823	Delayed resolution, pneumonia	Nothing	Greenish spot, 3x5 cm.
3	7944	Chronic bronchitis	Scarcely visible greenish spot	Same.
4	F7867	Tuberculosis, lung	Nothing	Nothing.
5	F7171	Epithelioma, face	Purplish spot, not raised, sharply defined, 2x3 cm.	Same but darker color.
6	F7898	Carcinoma peritoneum	Same appearance as No. 5	Same size but more green color.
7	F7715	Chr. art. rheumatism	Nothing	Nothing.
8	F6152	Epilepsy	Very light slate-colored spot	Same.
9	F4218	Tabes dorsalis	Slightly raised, purplish spot, 4x5 cm	Same.
10	F5999	Psoas abscess	Flat, slightly reddish spot	Slate blue spot, 3x4 cm.
11	F7817	Umbilical hernia	Slightly raised bluish spot, differs in color from Nos. 5 and 6.	Faint light green spot.
12	F7929	Cirrhosis liver	Nothing	Very faint light green spot.
13	F7925	Cirrhosis liver	Nothing	Very faint light green spot, 4x6 cm.

F refers to women; all others men.

seemed doubtful whether injections beneath the skin into the subcutaneous tissues would show through the skin. This at once raises the question of the value of a color reaction, for some skins are much thinner and more transparent than others. As the table shows, all such injections revealed marked discoloration. Again, it is doubtful if any large amount of plasma can come in contact with the injected red-cell suspension. The injection is a foreign substance, and the body cells must react toward it as they do toward any foreign substance. That some action does take place at times seems certain, because there are times when there is evidence that the hemoglobin of the injected cells has been released into the tissues. The curious "black-and-blue" spot simulating ecchymosis from a bruise seems to prove this. On the contrary, in certain persons the injected cells must be absorbed very quickly, for there is no evidence to reveal the injection. No explanation is offered for these phenomena.

It is evident from a perusal of Tables 1 and 2 that there is no regularity in regard to the hemolytic reaction. The statement of Weil is

TABLE 8.—SUMMARY OF SEVENTY-FOUR CASES FROM PREVIOUS TABLES

Disease	No. Cases	Pos.	Neg.	% Pos.	% Neg.
Carcinomas; epitheliomas	7	3	4	42.8	57.2
Rheumatic fever	5	1	4	20.0	80.0
Convalescent typhoid	8	4	4	50.0	50.0
Tuberculosis	9	3	6	33.3+	66.6+
Cirrhosis liver	3	1	2	33.3+	66.6+
Cancer liver, secondary	1	0	1	0	100
Sarcomas	2	1	1	50	50
Blastomycosis	1	1	0	100	0
All other diseases	38	10	28	26.3	73.7
Totals	74	24	50	32.4	67.6

borne out, namely, that human serum in various diseases is occasionally hemolytic toward the corpuscles of other human individuals. He was working with serum and corpuscles, but the same statement may be made in regard to hemolysis *in vivo*.

In Tables 3, 4 and 5 are shown the results of injecting 5 and 10 minims of suspension from 10 per cent. to 40 per cent. into the loose tissue of the mid-forearm and into the more adherent tissue near the wrist. No greater differences were noted than were found by using the recommended 5 minims of the 20 per cent. suspension. What differences there were, were so irregularly distributed that no information could be gained on the points noted above.

On the contrary, Table 6 seems to show that 10 minims of a 20 per cent. suspension caused more so-called positive reactions than 5 minims of a similar suspension.

This may have been simply a coincidence. At any rate, no importance is attached to it. This injection was given in the skin over the biceps.

There are seen fewer positive reactions in Table 7, using the same amount of a 20 per cent. suspension of blood from the same person, than in Table 6. In Observation 7 the suspension was injected into the forearm.

A total of all the injections shows that 67.6 per cent. were negative and 32.4 per cent. positive. In spite of the fact that tuberculous persons are said to possess more isohemolysins than normal persons, the figures of a few cases show 66.6 per cent. negative reactions. Leaving out the cases of malignant tumors, there are sixty-four cases with twenty positive and forty-four negative. This is quite different from the 94 per cent. negative reactions found in all other diseases by Elsberg, Neuhof and Geist.

In conclusion then, it seems evident that the same irregularities obtain in the hemolysis *in vivo* as that *in vitro*. The most evident point brought out is that the test cannot be said to be of any great value in the diagnosis of early carcinoma.

RECOVERY OF A TYPHOID BACILLUS-CARRIER DURING VACCINE TREATMENT *

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Medical literature during the past five years has contained numerous reports of chronic typhoid bacillus-carriers, but there has been very little discussion of the treatment of these patients. The reason for this paucity appears to be that treatment has been unsatisfactory, and in but few cases has the infection been eradicated.

Dehler[1] has cured by cholecystostomy two patients who discharged the bacilli in the feces, but the bacilli did not disappear from the stools of a paratyphoid carrier on whom Forster[2] did cholecystostomy for gallstones. Grimme[3] reported the recovery of an intestinal typhoid carrier on whom cholecystectomy was done. Park[4] failed to eradicate the infection in "Typhoid Mary," an intestinal carrier, by the use of intestinal antiseptics and hexamethylenamin; the latter drug was given in doses of 100 to 150 grains daily. Park cites Lentz, who stated that he could not get rid of the bacilli by any treatment. Albert[5] reported the disappearance of bacilli from the urine of a carrier treated with hexamethylenamin, but no details were given and no statement made as to permanent recovery. Niepraschk[6] had success with hexamethylenamin and boric acid (triborate of hexamethylentetramin) in the treatment of a urinary carrier after he had failed with hexamethylenamin alone and in combination with resorcin. He gave this preparation in doses of 1.5 gm. four times daily. Hammond[7] failed to cure an intestinal carrier to whom he gave hexamethylenamin for months.

Litterer[8] treated by vaccination a patient with a discharging typhoid bone lesion. He estimated that there were a half million bacilli in a

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*From the Medical Clinic of Colon Hospital, Cristobal, Canal Zone.

*Read in the Section on Practice of Medicine of the American Medical Association, at the Sixty-Second annual session, held at Los Angeles, June, 1911.

1. Dehler: München. med. Wchnschr., 1907, liv, No. 43.
2. Forster: Verhandl. d. deutsch. path. Gesellsch., 1907, p. 163.
3. Grimme: München. med. Wchnschr., 1908, lv, No. 1.
4. Park, W. H.: Jour. Am. Med. Assn., 1908, li, 981.
5. Albert, H.: Jour. Am. Med. Assn., 1908, li, 982. Discussion of Dr. Park's paper.
6. Niepraschk: Ztschr. f. Hyg. u. Infektionskrankh., 1909, lxiv, 454.
7. Hammond, F. S.: Jour. Am. Med. Assn., 1909, lii, 48.
8. Litterer, W. L.: Jour. Am. Med. Assn., 1908, li, 982. Discussion of Dr. Park's paper.

platinum loopful of the pus. He thought, justifiably, that the patient should be regarded as a chronic typhoid bacillus-carrier. Under vaccine treatment the patient showed great improvement, but was not entirely cured at the time of the report. He has recently informed us that this patient and another similar carrier were both cured by vaccination in three and two months, respectively.

Irwin and Houston[9] have successfully treated a urinary carrier by vaccination after failure with hexamethylenamin. The bacilli disappeared after the third dose and four subsequent examinations covering a period of two months were negative. Six vaccinations were given, the doses increasing from 50 to 1,000 million. Meader[10] treated successfully by vaccination a patient who discharged bacilli in her feces. The patient had had typhoid fever thirty years previously and had been exposed to infection five years previously. Before vaccination was begun, treatment was attempted with hexamethylenamin; 15 grains three times daily for two weeks were given, and then 75 grains daily. The large doses had to be discontinued after three or four days because of painful micturition. No diminution in the number of typhoid bacilli discharged in the feces could be detected. An attempt was then made to plant *B. coli* in the lower bowel in the hope that it would overgrow the typhoid organisms. Four doses, each about a pint, of a bouillon culture, were given per rectum. The typhoid organisms persisted in the stools and treatment with lactic acid bacillus tablets was tried; this also failed. Autogenous vaccines were then given at intervals of from one to two weeks. Six vaccinations were given, the doses increasing from 25 to 1,000 million, after which the stool cultures were negative on three separate examinations. Meader studied the bactericidal and agglutinating power of the blood during vaccination. The former rapidly rose, reaching its greatest power after 400 million bacilli were injected; it then fell rapidly, and seven days after 1,000 million bacilli were injected the bactericidal power had fallen to a point practically the same as when immunization work began. An interesting observation was that during the period of declining bactericidal power the agglutinating power became evident in dilutions of from 1 to 500 in one hour. The first stool examination that was found negative was seven days after the above phenomenon. No examination was made for twenty-three days previously, so it is difficult to correlate the disappearance of the bacilli with the serum phenomena. Meader seems inclined to think that the high bactericidal power of the serum was immediately correlated with the disappearance of the bacilli, but the stool was positive for bacilli only three days before the examination that showed the highest point of bactericidal power, and ten days after the previous

9. Irwin, S. T., and Houston, T.: Lancet, London, Jan. 30, 1909.
10. Meader, F. M.: Bull. Johns Hopkins Hosp., 1910, xxi, 280.

TABULATED DATA

Date.	Vaccin. Millions of Bacilli	Stool Cultures	Urine Cultures	Colonies per Loopful	Loopfuls of Urine Used	Agglutination Tests					
						Stock Culture			Urine Culture		
						Dilution Serum	Reaction	Time (hrs.)	Dilution Serum	Reaction	Time (hrs.)
9/22/10	....	—	—	...	.....	.....	..	..	.....	..	..
10/4/10	....	—	..	...	.....	.....	..	..	.....	..	..
10/7/10	....	—	+	+†	.....	1-40	±	1	1-40	+	1
10/10/10	25	..	..	...	.....	.....	..	..	.....	..	..
10/11/10	....	—	..	...	.....	.....	..	..	.....	..	..
10/15/10	....	..	+	+†	.....	1-50	±	1	1-40	±	1
10/19/10	50	..	..	...	.....	.....	..	..	.....	..	..
10/26/10	....	..	+	+†	.....	1-50	—	1	1-50	+	1
10/28/10	100	..	..	...	.....	.....	..	..	.....	..	..
11/4/10	....	..	+	+†	.....	1-50 1-100	+ +	1 6	.....	..	..
11/6/10	150	..	..	...	.....	.....	..	..	.....	..	..
11/16/10	200	..	+	+†	.....	1-50 1-200	+ +	1 2	.....	..	..
11/26/10	250	..	+	92	3	1-100 1-250	+ +	1 2	.....	..	..
2/6/10	400	..	+	18	3	1-500	+	3	.....	..	..
12/9/10	....	..	+	45	3	.....	..	..	1-50 1-200 1-300	+ + ±	1 2 2
12/17/10	....	..	+	32	3	1-150 1-1000	+ +	1 6	1-150 1-300 1-400	— + ±	1 6 6
1/3/11	....	..	+	5	3	1-150 1-200	+ ±	6 6	1-150 1-200	+ —	6 6
1/10/11	1000	..	..	...	.....	.....	..	..	1-50	+	1
1/21/11	....	..	+	2	3	1-150	±	.. 1	1-150 1-200	+ ±	1 1
2/1/11	1500	..	..	...	.....	.....	..	..	.....	..	..
2/11/11	....	..	?	...	3	1-400	+	5	1-400	+	5
2/15/11	....	..	—	0	3	1-1000	+	6	1-1000	+	6
2/20/11	....	..	—	0	0.2 c.c.	.....	..	..	.....	..	..
2/28/11	....	..	—	0	0.2 c.c.	.....	..	..	.....	..	..
3/1/11	....	..	..	...	.....	1-1000	+	6 1	1-600 1-1000	+ ±	6 6
3/24/11	....	..	—	0	2 c.c.§	1-200 1-400 1-800	+ + —	4 19	.....	..	..
5/2/11	....	..	—	0	10 c.c.§	.....	..	..	.....	..	..

• Forty typhoid-like colonies per loopful of urine. A transplant from one colony proved it to be *B. fecalis alkaligenes*. Colonies of *B. coli* were also present. We thought it probable that all the colonies were contaminations and decided to make other cultures from a more carefully obtained urine.

† Numerous. § Bouillon inoculated and plates made from bouillon cultures.

examination. The bacilli disappeared some time during a period of twenty-three days that covered the maximum point and the rapid decline of bactericidal power and the rise and fall of agglutinating power. Our experience with our own case leads us to suggest that the phenomena were coincidences, and that the disappearance of bacilli was due to the healing of a chronic lesion under the influence of vaccination — that the healing was completed coincidentally with the serum phenomena.

Cummins, Fawcus and Kennedy[11] treated six typhoid carriers and one paratyphoid A carrier. Two of these were urinary carriers and five intestinal. They used implantation of *B. bulgaricus;* they tried intestinal and urinary antiseptics, including hexamethylenamin (urotropin) alone and together with another diuretic; they attempted to influence the infection by acidifying the urine by means of the administration of sodium benzoate and acid phosphate of soda; they exposed the gall-bladder and kidneys to *x*-rays; and they vaccinated three patients with stock and autogenous vaccines.

One intestinal carrier recovered during the administration of *B. bulgaricus* in large doses, but others were not improved by it. An intermittent intestinal carrier ceased to discharge bacilli on two occasions after exposure of the gall-bladder to the *x*-rays, and the bacilli were not found in his stools when he was discharged from observation. It was thought, however, that this absence of bacilli might be due to a natural intermission rather than to cure by treatment. Bacilli in the feces and urine respectively of two other patients decreased in numbers after *x*-ray treatment, but increased again when treatment was discontinued. Antiseptics reduced the number of bacilli but when antiseptics were discontinued the number rapidly rose. Vaccination was carried out on three patients, one an intestinal carrier, two urinary carriers. It failed in all three cases to eradicate the infection.

The authors are sure, therefore, of the recovery of only one patient during treatment, an intestinal carrier treated with lactic acid bacilli (*B. bulgaricus*). They think that a combination of vaccination with hexamethylenamin in urinary carriers, and of vaccination with *x*-rays in gall-bladder intestinal carriers may prove to be effectual.

Stone[12] has reported one typhoid carrier treated by vaccination. His patient was a urinary carrier, and recovered during treatment with autogenous vaccines. Six doses, increasing from 100 to 400 million, were given, and stool cultures were negative after the sixth dose.

To sum up, three chronic intestinal typhoid carriers have recovered after operations on the gall-bladder. One urinary carrier has recovered

11. Cummins, S. L.: Fawcus, H. B., and Kennedy, J. C.: Treatment of Typhoid Carriers, Jour. Roy. Army Med. Corps, Lond., 1910, xiv, 351.
12. Stone, W. J.: Jour. Am. Med. Assn., 1910, lv, 1708.

during the administration of hexamethylenamin in combination with boric acid (triborate of hexamethylentetramin). One intestinal carrier recovered when lactic acid bacilli (*B. bulgaricus*) were implanted in the alimentary tract. One intestinal carrier apparently recovered after repeated exposures of the gall-bladder to *x*-rays. One intestinal carrier, two urinary carriers, and two carriers discharging bacilli from bone lesions have recovered during vaccination with autogenous vaccines. We shall add to the number one urinary carrier that recovered likewise during vaccination with autogenous vaccine. Altogether then, there have been only twelve recoveries of typhoid carriers as far as we have been able to find; six recoveries of intestinal carriers, four of urinary carriers and two of carriers with bone lesions. Including our own patient, six have recovered during treatment with autogenous vaccines.

CASE REPORT

Our patient was a little American girl, white, aged 4½ years. She had had an attack of fever, that was probably a mild initial attack of typhoid, in July, 1910, during which she was not under our care. She was admitted to Colon Hospital (No. 26,236) Aug. 3, 1910. She had a typical uneventful rather mild attack of typhoid fever, during which her serum in 1 to 50 dilution agglutinated the stock culture of *B. typhosus* in one hour. During the last fourteen days of convalescence she was given for prophylactic reasons 3 grains of hexamethylenamin three times daily—rather large doses for a small child. She was discharged from the hospital Sept. 3, 1910.

On September 18, the child's mother was admitted to the hospital with continued fever, the onset having been about three days previously, or twelve days after the child's return home. *B. typhosus* was isolated by blood culture. The course of illness was typical of a rather severe attack of typhoid fever.

On September 19, the child's father was admitted with a mild remittent fever that persisted ten days, maximum 101.5 F. The onset of his attack was September 16, or thirteen days after the child's return home. A blood-culture, made after six days of fever and four days before the temperature remained normal, was negative. Although the patient had never had typhoid fever, two agglutination tests by Bass[13] macroscopic method were positive. There appeared a few quite definite rose spots. The spleen was not palpable. In the light of these facts and of subsequent events, it is quite certain that this was a mild attack of typhoid fever.

These two cases led us at once to suspect that the child was discharging typhoid bacilli in her urine or feces, and that she had infected her father and mother. Four examinations of her stools were all negative for *B. typhosus*. On the first attempt we failed, also, to obtain *B. typhosus* from the urine, but the second culture, Oct. 7, 1910, was positive, and the organisms were isolated ten times thereafter without a failure until they finally disappeared, Feb. 15, 1911, about six months after the attack of typhoid fever was over. Five successive negative examinations, covering a period of about three months, were then made.

Vaccination with autogenous vaccines was begun on Oct. 10, 1910, and nine doses, increasing from 25 to 1,500 million, were given, the last on Feb. 1, 1911, after which typhoid bacilli could no longer be isolated from the urine. The bacilli gradually decreased in numbers as vaccination proceeded. The first vaccine used (seven doses) was sterilized at 60 C. for one hour; the second vaccine (two doses), at 53 C. for one hour. The vaccinations gave slight local reactions

13. Bass, C. C.: THE ARCHIVES INT. MED., 1910, vi, 717.

only until the last injection of 1,500 million bacilli, when a mild general reaction occurred. The injection was given about 10 a. m., February 1, and at 8 p. m. the patient's temperature was 102. By noon the next day, the temperature had reached normal. During the entire time the patient seemed in perfect health.

Numerous agglutination tests were made before, during and following the vaccination period. Before vaccination the patient's serum in a 1-to-40 dilution gave a positive reaction in one hour against a suspension in salt solution of a twenty-four-hour agar culture of her own organisms, and an incomplete reaction against the bacilli of a stock culture. Three days after the first vaccination the reaction against both strains was incomplete. Seven days after the second vaccination, a 1-to-50 dilution of serum agglutinated the urine culture in one hour, but the reaction was negative in one hour against the stock culture, which, however, was agglutined in six hours by dilutions of serum up to 1 to 200. After the seventh vaccination (400 million bacilli), the serum in a 1-to-150 dilution agglutinated the stock culture in one hour, and in six hours the stock culture was agglutinated by a 1-to-1,000 dilution. At this time a 1-to-150 dilution of the serum failed to agglutinate the urine culture, and in six hours the maximum dilution that caused agglutination was 1 to 300. Vaccination was then suspended for thirty-five days, during which the agglutinating power of the serum decreased. After twenty-eight days a 1-to-150 dilution of the serum agglutinated both strains in six hours, but in the same time a 1-to-200 dilution gave an incomplete reaction against the stock culture and was negative against the urine culture. Vaccination was resumed Jan. 10, 1911, and on Jan. 21 a 1-to-150 dilution of serum agglutinated in one hour the urine culture, but gave an incomplete reaction against the stock culture. On Feb. 1, 1911, the last vaccination (1,500 million bacilli) was given, and on February 15 the serum in a dilution of 1 to 1,000 agglutinated both organisms in six hours. On March 1, a 1-to-1,000 dilution still agglutinated the stock culture in six hours, but the reaction was incomplete against the urine culture. On March 24, nearly two months after the last vaccination, the serum in a 1-to-200 dilution agglutinated the stock culture in one hour, and a 1-to-400 dilution, in four hours.

Between the dates of Dec. 6, 1910, and Jan. 10, 1911 (see table), no vaccinations were given, and the agglutinating power of the serum against both the urine culture and the stock culture decreased. On December 17, a 1-to-1,000 dilution of serum was positive in six hours against the stock culture, but a 1-to-300 dilution was the maximum dilution positive against the urine culture. On January 3, a 1-to-200 dilution gave in six hours an incomplete reaction against the stock culture and a negative result against the urine culture. During the period of this decreasing agglutinating power of the serum, the number of bacilli in the urine not only failed to increase, but actually decreased from 32 per loopful of urine on December 17 to 5 per loopful on January 3.

At the time of the observations no records were made of the numbers of colonies on the plates, but our impression is that during the first two months the number remained approximately the same. On November 26, there were 92 colonies per loopful of urine, and, with one exception, the number decreased gradually thereafter—92, (18), 45, 32, 5, 2, 0.

Nov. 26, 1910	92 colonies per loopful
Dec. 9, 1910 (13 days' interval)	45 colonies per loopful
Dec. 17, 1910 (8 days' interval)	32 colonies per loopful
Jan. 3, 1911 (17 days' interval)	5 colonies per loopful
Jan. 21, 1911 (18 days' interval)	2 colonies per loopful
Feb. 11, 1911 (21 days' interval)	0 colonies per loopful

If the time intervals are all changed to two weeks and the number of bacilli are calculated for each examination according to the rate of decrease for each period, the following results are obtained: 92, 42, 20, 4, 2, 0. In other words, the decrease in the number of bacilli proceeded with almost mathematical precision, the number being reduced one-half every two weeks, excepting during the

third interval, when reduction was more rapid. A part of this reduction was not associated with an increasing agglutinating power of the blood serum, but with a decreasing power; nor did the reduction cease when the agglutinating power rose again with subsequent vaccination. The phenomena suggest strongly that antibodies produced by vaccination were not acting on bacilli in the urine, but that a chronic typhoid lesion that was discharging typhoid bacilli in the urine slowly healed under the influence of vaccination, probably as the result of the action of antibodies in the lymph or exudate on the bacilli in the lesion. That there were not antibodies sufficient even to inhibit growth in the urine was shown by inoculating the sterile urine, just after the disappearance of typhoid bacilli, with typhoid organisms from both the stock and urine cultures. Both organisms grew well, in spite of the fact that the agglutinating power of the blood serum at this time was 1 to 1,000 in six hours.

Our experience leads us to suggest, therefore, that the eradication of the infection of chronic typhoid carriers by vaccination is brought about by the gradual healing of a chronic lesion under the influence of antibodies produced by the vaccination. If the bacilli grow in secretions and excretions only, it does not seem that vaccination would be effectual. Hexamethylenamin or lactic acid bacilli might be effectual in such cases. The only other treatment that our patient received was four 5-grain doses of hexamethynamin on December 6 and 7. The previous examination of urine, November 26, had shown 92 bacilli per loopful. This result had discouraged us, and we brought the patient to the hospital to give a trial to hexamethynamin treatment. We obtained a specimen of urine and began hexamethylenamin treatment before the plates were incubated. On the following day, we found the number of colonies so reduced that we discontinued hexamethylenamin and resumed vaccine treatment. That the four doses of hexamethylenamin had no permanent effect on the bacilli was shown by the fact that the number of organisms was 45 per loopful two days after the drug was given.

There may be a question as to whether or not our patient should be considered a chronic typhoid carrier. According to the classification of Frosch,[14] she should be considered one. Frosch divided carriers into two groups: "those who excrete bacilli for less than three months, and those who excrete them for three months and longer. The latter class constitute the chronic bacilli carriers, the *Dauerausscheidern* of the Germans" (Simonds). Our patient carried typhoid bacilli for about six months after the temperature of her typhoid attack remained normal, and, accepting Frosch's classification, she may be considered fairly as having been a chronic typhoid bacillus carrier.

The possibility cannot be denied that the lesion that discharged bacilli may have undergone spontaneous healing without regard to vaccination. We prefer to say, therefore, that our patient recovered during vaccination, rather than that she was cured by the treatment. In the light of what is known of chronic typhoid carriers and of the chronicity of post-typhoid lesions, however, it does not seem probable that recovery was spontaneous.

One other objection might be made. Some typhoid carriers, both urinary and intestinal, discharge the bacilli intermittently. It may be suggested with reason that the disappearance of bacilli in our case may have been due to an intermission. This is possible. But the bacilli were

14. Frosch: Klin. Jahrb., 1908, xix, 537. Cited by Simonds, J. P.: Am. Jour. Med. Sc., Aug., 1910, cxl, 247.

present on eleven successive examinations covering a period of more than three months, they gradually decreased in numbers and finally disappeared, and they have been absent on five successive examinations covering a period of almost three months. The first urine examination made was negative for typhoid bacilli, but the result was probably due to faulty technic, for we had just begun making bacteriological examinations of stools and urines. It seems probable to us, therefore, that our patient was a continuous chronic typhoid carrier, and that she made a permanent recovery during treatment with autogenous vaccines.

BACTERIOLOGICAL CONSIDERATIONS

Isolation.—The method of isolation of typhoid bacilli from the urine was that of Endo.[15] Endo's medium is a heavy agar to which is added basic fuchsin, lactose and sufficient sodium sulphite to decolorize the fuchsin. The red dye, fuchsin ($C_{20}H_{19}N_3HCl$), is an acid salt of rosanilin, a colorless leukobase. The acid component of the red rosanilin salt is easily reduced by sodium sulphite. When lactose-fermenting organisms grow on the above medium, the acid formed combines with the decolorized rosanilin and the colonies are stained red. The heavy agar medium is exactly like "ordinary" agar, excepting that 20 gm. of agar-agar per 1,000 c.c. are used instead of 15 gm. To 1,000 c.c. of the agar medium are added: lactose, 10 gm.; basic fuchsin, 1.8 c.c. of a 10 per cent. solution in alcohol; sodium sulphite, 25 to 40 c.c. of a 10 per cent. aqueous solution. The sodium sulphite should be added until the red color has changed to a faint pink. The agar medium can be prepared in bulk to be kept in stock, but the fuchsin, lactose and sodium sulphite should be added just before pouring into the plates. One hundred cubic centimeters of the medium will make about four or five plates, which should be 12 to 15 cm. in diameter. The plates are exposed to the air (covered with clean paper), for one hour, during which they harden and dry. One loopful or more of the material to be examined is then placed on the surface of the first plate, and with a sterile bent glass rod it is spread widely over the surface; the rod is then stroked over the surface of the second plate; then the third, and so on. The plates are covered, wrapped in paper to exclude light, and incubated for twenty-four hours. The colonies of the lactose-fermenting organisms are then red, while the colonies of non-lactose-fermenting organisms are colorless. The method thus furnishes an easy way of isolating typhoid, paratyphoid and dysentery bacilli. The organism that causes difficulty most frequently is *B. fecalis alkaligenes.*

15. Endo: Centralbl. f. Bakteriol., 1904, xxxv, 109. A transcription of Endo's article was kindly given us by Dr. S. T. Darling, chief of the Board of Health Laboratory, Ancon, Canal Zone.

Identification.—The organisms that we isolated from the urine were small, actively motile, Gram-negative bacilli. They formed small, 1 to 2 mm. diameter, translucent colonies with a bluish refractility on agar plates. Litmus milk was slightly acidified by them and remained acid. There was an invisible growth on potato. No indol was formed in Dunham's peptone medium. Bouillon showed a general turbidity without pellicle or sediment. There was no gas formation in any of the semi-solid litmus sugar media; acid formed in dextrose, mannite, galactose and dextrin; there was no change in lactose, saccharose or dulcite. The organisms were agglutinated by the serum of a typhoid patient (the child's mother) in a 1-to-50 dilution in one hour. After the child was vaccinated with her own organisms, her serum agglutinated a stock culture of typhoid bacilli in a 1-to-200 dilution in one hour and in a 1-to-1,000 dilution in six hours.

SUMMARY

1. The literature of the treatment of typhoid bacillus-carriers is reviewed. Eleven recoveries, excluding our case, have occurred. Five of these patients recovered during vaccination with autogenous vaccines.

2. Our patient was a white child, female, aged 4½ years. Shortly after her attack of typhoid fever, her father and mother were infected. Typhoid organisms in pure culture were isolated from the child's urine. Hexamethylenamin had been aministered to the patient during two weeks of convalescence from the typhoid attack.

3. Practically the only treatment given was vaccination with autogenous vaccines. Nine doses were given, increasing from 25 to 1,500 million. The bacilli decreased gradually and disappeared after the ninth vaccination. Eleven successive urine cultures were positive for *B. typhosus* and then five successive cultures were negative.

4. The total duration of the bacilluria, from the time of normal temperature, was about six months. The patient appeared to be a continuous carrier.

5. It seems that the disappearance of the bacilli was not an intermission but a true recovery, brought about by the gradual healing of a chronic lesion under the influence of vaccination.

We wish to thank Col. W. C. Gorgas, Chief Sanitary Officer, for permission to publish this report.

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SUBACUTE LIVER ATROPHY *

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Since the time of Vesalius (1514-64) a great profusion of types of liver disease have been described and each associated with a more or less definite train of symptoms, till the present time leaves us with the most confused ideas of the pathological processes at work in almost any case of jaundice. As a result, the diagnosis of cases of long-continued jaundice, exclusive of those due to such obstructive causes as gall-stones, tumor growth, etc., leads inevitably into the tangled artificial classification of the various destructive lesions of the liver.

One fact is certain—that in the whole range of diseases of the liver, from acute yellow atrophy to atrophic cirrhosis, the cases present an extreme variation as regards duration, symptomatology and morbid anatomy; and it may equally be noted that great numbers of cases present features which preclude them from any of the usual subdivisions of liver disease.

Acute yellow atrophy, as is well known, is an extremely wide-spread rapid necrosis of the liver. The term "atrophy" is therefore a misnomer. The condition is certainly much more common than it has usually been considered and this perhaps is accounted for, as in the past its conception has been based on an altogether too classic picture both clinically and pathologically. The disease has, however, a wide latitude in its duration, clinical type and pathological appearances and the condition appears to be essentially dependent on the degree of hepatic destruction. Examples indicating the discrepancy in the tenure of life in such cases may be noted in records reported by Ladoli in which death occurred in thirty hours, Dörfler, in three days, Fischer, in ten days, Edgworth, in twelve days, McCallum, in fourteen days, Tileston, in seventeen days, Hall, in twenty days, Meder, in twenty-one days and Klob, in twenty-eight days, etc.; and many cases are described of as long as forty days' duration. In children in particular, a protracted course is the rule. (In a previous communication[1] I have noted three cases in young children who presented histories varying between six and ten weeks, and I have observed two other cases which came to autopsy after a considerably more prolonged course.)

The latter merge gradually into what may be known as the subacute group, in which the subject apparently has had more recuperative power and the hepatic destruction has not been so extensive. Thus, if the destructive processes, from whatever source, chemical, bacteriologic, etc.,

*From the Russell Sage Institute of Pathology, New York.

1. Milne, Lindsay S.: Jour. Path. Bacteriol., Cambridge, 1909, xiii, 161.

they may be derived, should be less extensive in their effects on the liver, the symptomatology corresponds more or less in degree.

Not only is the extent of liver destruction important but also the rapidity of its accomplishment. In atrophic cirrhosis for instance, the process is also wide-spread but as such relatively small portions are destroyed at one time, and also as the liver cells have time to regenerate and the system to adapt itself, jaundice does not necessarily appear.

Subacute atrophy, like acute yellow atrophy, is not a real atrophy, but the result of a necrosis and the subsequent inflammatory repair. As in the acute cases, the necrosis is more or less rapidly accomplished, and the longer duration of life in the subacute or recovery in the chronic cases depends largely on the amount of liver destruction and its recuperative power.

Age and sex apparently are of little importance, acute and subacute atrophy being relatively common in children; thirteen patients observed in the last three years varied in age between 4 years and 69.

The etiology of such conditions has occasioned a vast amount of speculation; the disease seems to follow so many conditions, to be so widely different in its clinical and pathological types, as to make one suspect no uniform etiological agent. Some cases show no apparent toxic substance in the liver, being sterile in culture, and emulsions of the liver being nontoxic to rats, rabbits or cats; as for instance, in a male, aged 69, who died after a progressively intense jaundice of twelve days' duration. In another case, slightly more protracted, in a male aged 38, in which death occurred in an intensely jaundiced condition, a pure culture of *B. coli* was obtained from the liver and spleen. Emulsions of the liver and spleen injected into rats produced death within twenty-four hours, while injections of emulsions from the duodenum and large intestine produced no effect. A pure *B. coli* was again isolated from the livers and spleens of the dead rats, which again proved fatal to another series of rats, but produced no result on rabbits, dogs or cats. This, however, means very little as a variety of organisms can be obtained from the livers of subjects who have died from many different causes.

REPORT OF CASE

From an experience of ten cases in the last three years, five of which have already been published,[1] presenting histories lasting six weeks and upward, a further case may be noted in which the process was very prolonged and the diagnosis from ordinary cirrhosis presented difficulties even at necropsy.

History.—The patient was a large, obese man, aged 41, a bar porter. His previous health and digestion had been apparently very good. He had been in the habit of drinking two or three glasses of whisky a day. There was no evidence or history of syphilis, nor any indication of it in his family record. He denied malaria, scarlet fever, diphtheria, small-pox, pneumonia, typhoid or any other special disease.

Sixteen months before the date of his death, his ankles became slightly swollen in the evenings. This swelling disappeared when he rested at night and was never sufficient to incapacitate him from his work. Six months after this, jaundice gradually appeared, although he felt at that time in very good health. A fortnight later, the jaundice suddenly became very intense, and there was marked distress in the epigastric region. This was diffuse in character and not colicky or related to the shoulder region, and was not associated with any gastro-intestinal disturbance. Immediately following this attack, and being as he said, not under the influence of liquor, he became very much prostrated and fainted. On admission to hospital he was intensely jaundiced, and the urine contained a considerable amount of bile pigment but no albumin, leucin or tyrosin. His heart was somewhat irregular in action, and there was a soft systolic murmur heard, best at the region of the apex. He remained in hospital for two months, his weight remaining constant and the temperature continuing normal. The jaundice almost completely faded and he was discharged, feeling in good condition. Six days later he was readmitted, as edema of the legs had returned and jaundice had again become intense. Ascites was also slightly evident. The liver at this date extended from the sixth right costal interspace to 1 inch below the costal margin in the right midclavicular line. Its lower border was firm and rather irregular and on palpation was slightly tender. The spleen was palpable 1 inch below the left costal margin, and a soft, systolic murmur was noted over the apex of the heart. The blood showed no important changes except slight anemia, and the urine contained no albumin, but bile was present in small quantity. The feces were pale but did show some bile-coloring. About a month later the patient developed a mild attack of facial erysipelas. For the next six months the jaundice continued, gradually growing more intense. The temperature, except for some small irregularities and during the attack of erysipelas, was practically normal throughout. The leukocyte count averaged about 5,000 per cubic millimeter, rising to 14,600 coincidentally with the erysipelas. Ascites became very marked and the patient was tapped fifteen times during the last six months, large quantities of somewhat bile-stained clear fluid averaging 1.010, specific gravity being removed. During the last month, the stools were quite clay-colored, the patient's appetite completely failed and emaciation was rapid. His abdomen was tapped twice within the last ten days, and on both occasions the fluid withdrawn was turbid from the presence of pus cells. Toward the end he developed typical signs of acute general peritonitis and died in an extremely prostrated state, being also very intensely jaundiced at this time.

Macroscopic Pathologic Examination.—At necropsy the peritoneal cavity contained a large amount of turbid fluid. The peritoneum was uniformly covered by a delicate fibrinous exudate and also generally thickened. The exudate was particularly purulent over the liver, in the pelvis and in the region of the sigmoid. The intestines were distended and edematous.

The spleen (weight 525 gm.) was considerably enlarged, dark and firm. The kidneys (weight left 275 gm., right 285 gm.) were slightly enlarged, congested and showed a slight degree of chronic nephritis.

The pancreas was atrophic and there was also a mild degree of interstitial pancreatitis.

The heart (weight 350 gm.) was atrophied and dilated in all its chambers but showed no interstitial myocarditis. The aorta and larger vessels were well preserved.

The gall-bladder was small and contained a little watery brown bile. The glands along the bile-duct were slightly enlarged and considerably jaundiced.

The liver weighed only 700 gm. and measured 25 cm. laterally, 5 cm. in thickness. Its surface for the most part was pinkish and smooth, but over the upper part of the right lobe and the under-surface on both sides, near the hilum and also in the Spigelian lobe were numerous elevated brown nodules. These nodules varied in size from that of a millet-seed to 1 cm. in diameter. On section, the liver-tissue seemed to be almost entirely replaced by dense fibrous tissue. In the central portion of the organ in particular, there seemed to be almost no

liver-tissue remaining (Fig. 1). The larger vessels of the liver showed no special gross exchange nor were there any evidences of thrombosis. The islets of liver-tissue were brown, well defined but somewhat irregular in outline. They varied in size up to several which reached 2 cm. in diameter. These islets appeared quite homogeneous in character, although the larger ones were intersected by a delicate fibrous stroma. They had lost the characteristic lobular markings.

Microscopic Pathologic Examination.—The brown areas were composed of liver-cells which for the most part were crowded together and had lost their trabecular and lobular arrangement. These liver-cells were also somewhat irregular in size, many being very large and hypertrophic, and some were noticed to contain several nuclei. In this particular case, the process was of such long duration that signs of active liver-cell multiplication were wanting. No mitoses were observed, although some evidences of amitotic nuclear division could be noted. Yet the irregularity of the liver-cells, and particularly their large size, indicated that some hyperplasia had occurred previously. Contraction of fibrous tissue round islets of liver-cells does not, as a rule, produce the appearances of compression which are common around tumors and in congenital syphilitic cirrhosis, and certainly is not responsible for the appearances described as due to liver-cell hyperplasia. These nodules of liver-cell hyperplasia were comparatively small, but in some cases they tend to assume very large dimensions. Two such cases I have seen diagnosed and operated on as abdominal tumor growths. (In this connection, Barbacci[2] reports an interesting case of subacute atrophy in a woman whose liver was extensively cirrhotic and showed a tumor, composed of hyperplastic liver-cells the size of a fetal head projecting on the right lobe, and another the size of a Tangerine orange on the surface of the left lobe.)

In this case the fibrous tissue was very dense but contained only a small proportion of elastic tissue. Included in this, there were numerous small islets of closely packed liver-cells which apparently had escaped destruction and had proliferated considerably. Bile-ducts were fairly numerous, but in certain areas none were obvious at all. Many of these ducts communicated directly with the liver-cells, and others also could be traced to old persisting interlobular bile-ducts.

By serial sections, the course of the "ducts" could be traced more satisfactorily. For the most part they pursued a definite course between liver-cells with which they were directly continuous and some definite interlobular bile-duct. Many of these "ducts" connected with the liver-cells or interlobular bile-ducts ended blindly, but they mostly formed part of an extremely interlacing network. This network, which could be reconstructed from serial sections, seemed to be very similar in general distribution to the normal drainage system of the liver (compare Fig. 2) although naturally considerably distorted by the inflammatory tissue through which the ducts extended. When the complexity of anastomosis and accuracy of relationships of this reconstructed system was considered, it was apparently impossible that either liver-cells or bile-ducts could have produced these structures by proliferation.

Evidences of proliferation of liver-cells in those areas which have survived are common in all destructive processes of the liver and are particularly marked in the extensive lesions of acute and subacute atrophy and in all the forms of cirrhosis. In these areas, the multiplication and hypertrophy of liver-cells corresponds to the appearance which can be induced by experimental removal of large quantities of the hepatic tissue.[3] As in experimental cases, the multiplication of liver-cells is much more frequently produced by a process of amitosis than by karyokinesis, which seems to occur as a relatively early phase in the process of liver-cell multi-

2. Barbacci: Beitr. z. path. Anat. u. z. allg. Path., 1901, xxx, 45.

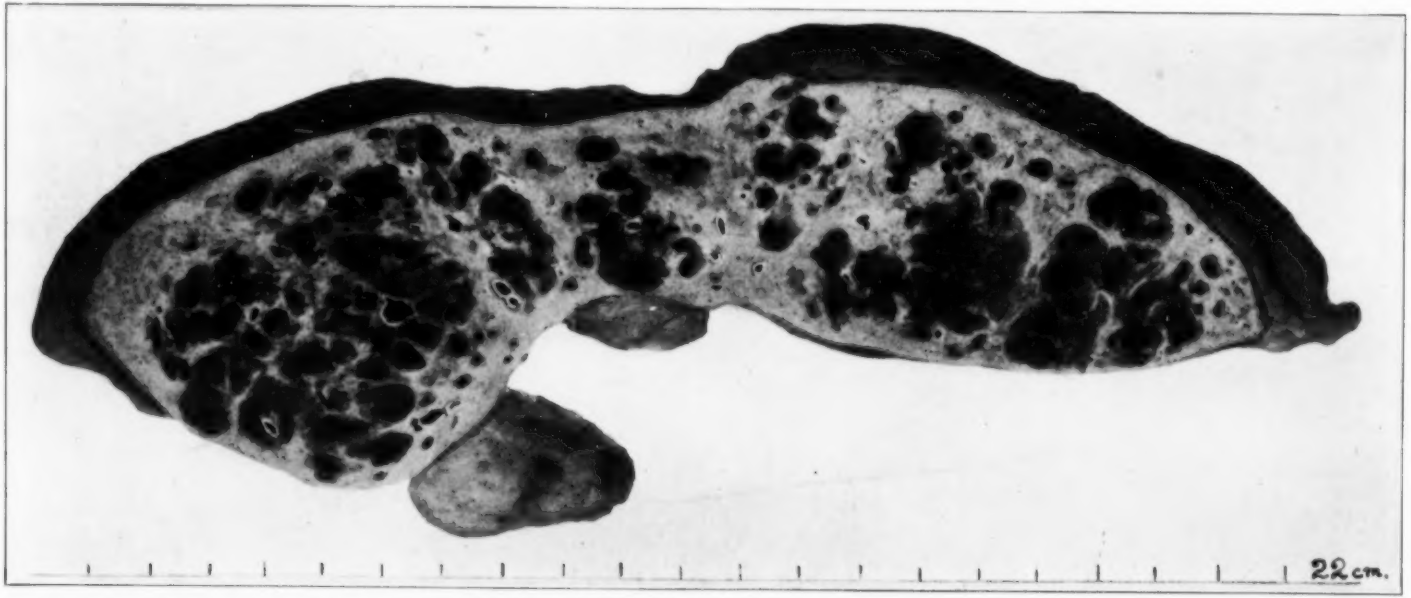

Fig. 1.—Section through the center of the liver, showing very extensive fibrosis and hyperplastic nodules of liver-cells.

plication. Mitotic figures in the liver-cells are common in many degenerative and necrotic conditions of the liver. I have seen them in enormous quantities in a case of lymphadenoma. Yet, in the same cases, coincident with the karyokinetic process, amitotic cell division is also taking place and in the later stages of repair seems almost entirely to predominate.

Although connections with "ducts" are common in such cases and evidences of liver-cell hyperplasia very marked, yet definite appearances suggesting a proliferation of these "ducts" from liver-cells are altogether wanting. The "ducts" so commonly found in new inflammatory tissue in the liver are also commonly directly connected with interlobular bile-ducts. As in the case of the liver-cells, no definite proof can be observed that the new "duct structures" are proliferated outward from some pre-existing interlobular bile-duct.

Catarrhal proliferative changes are common in the lining epithelium of the bile-ducts, both large and small, in almost all acute conditions affecting the liver, and can be induced experimentally by injection of the bile-ducts, or by inoculation of many toxic substances which seem to act chiefly by their irritative or destructive action in course of elimination down the bile-passages. The bile-duct epithelium, indeed, seems to have a very remarkable capacity for repair, as was shown by Serafini, who studied the regenerative capacity of the gall-bladder epithelium of guinea-pigs after its removal by a pad of cotton wool, the new cylinder epithelium being completely restored by the eighth day. This catarrhal proliferation does not, however, seem to have any tendency to induce sprouting from the ducts in the shape of the new "duct structures" so commonly found in inflammatory conditions of the liver.

Judging from the definite connections of these "ducts," their very definite and regular structural characteristics, and perhaps chiefly from their formation in a definite reticulum which more or less corresponds to the normal drainage liver system, it seems probable that they represent the normal surviving bile canaliculi connecting the liver-cells with the larger bile-ducts. In its new environment of inflammatory tissue, their epithelium from which the liver-cells have been denuded by necrosis, has become more cubical than the normal extremely flattened, almost invisible type. Analogies of this supposition are to be found in other organs, as for instance, the lining epithelium of the air alveoli in chronic inflammatory conditions in the lung and also in Bowman's capsule in the kidney in various types of chronic nephritis.

In the above-described case of subacute atrophy, there were several spots, and particularly one large area, where this idea could be somewhat substantiated. In these places there was an adenomatous arrangement of ducts (Fig. 3). For the most part, the duct spaces were continuous, widely dilated and in part, or altogether, lined by a cubical epithelium.

3. Milne: Jour. Path. and Bacteriol., Cambridge, 1909, xii, 146, Plate xx.

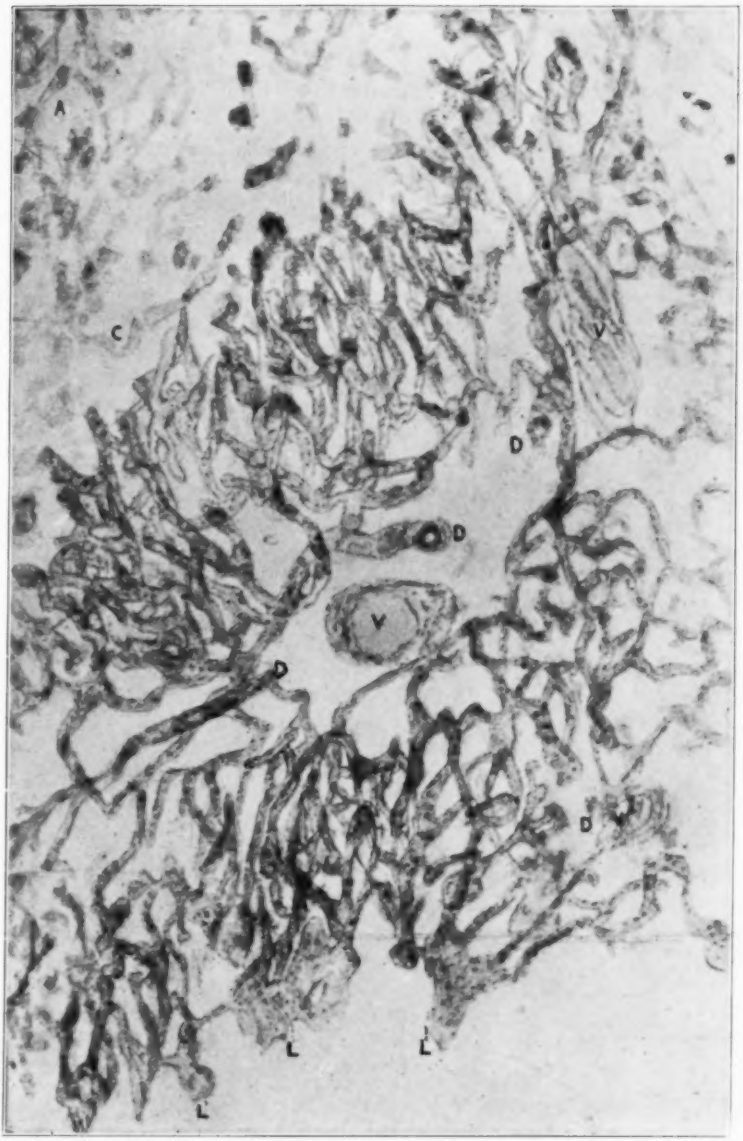

Fig. 2.—Reconstruction of a section of a subacute liver atrophy in a child 8 years old, who had suffered from jaundice for two months, commencing seven months before death, and during the last month slight jaundice had reappeared with also some ascites. This represents twelve sections each 10 microns thick. A certain spot in each was photographed, the positive plates of these superimposed, and a photograph taken of the whole. All the structures can be seen to have very definite relationships. V, V^1 and V^2 are portal veins. D, D^1 and D^2 represent interlobular bile-ducts; L, Liver-cells. An intricate ramifying system of ducts, connects the liver-cells with the interlobular bile-ducts, but many of the ducts also end blindly, where the liver-cells with which they should connect become destroyed. A represents the system surrounding an adjacent portal tract. The liver-cells between these two systems have disappeared and the two portal tracts with thir surrounding inflammatory zones have become contiguous. In only a few situations, as at C, do the two groups anastomose.

Many, however, were lined by an extremely attenuated type of cell and in parts a thin line of protoplasm containing no nuclei, alone formed the lining of the space. In several spots at the margins of these areas, columns of liver-cells were directly continuous with this adenomatous formation. It was a question whether these liver-cells were evolved as a metamorphosis or proliferation from the "duct" structures or *vice versa*, but more probably they were only surviving liver-cells maintaining connections with their original bile-discharging system which for some reason, obstructive possibly, had become distended.

Subacute atrophy, then, may be considered as a more protracted stage of the acute condition when the subject has been more resistant and the destructive process less extensive. There may thus be types of every

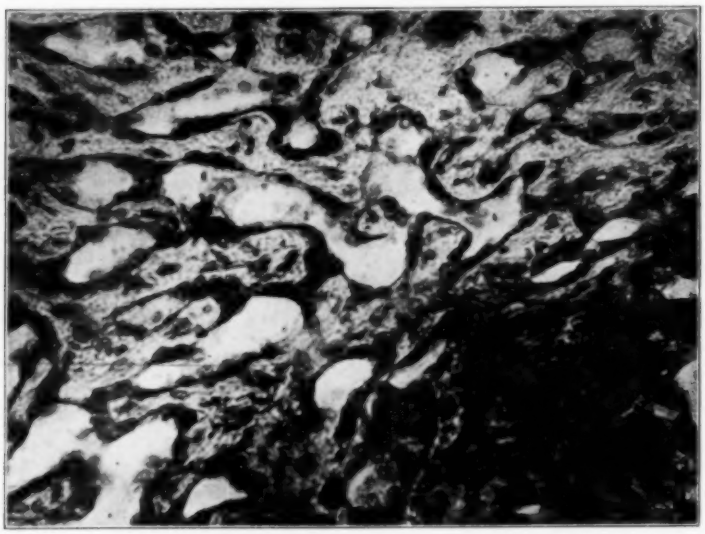

Fig. 3.—Area showing numerous adenomatous bile-ducts. The lining of the spaces is in some partly cubical and in others very attenuated. Toward one corner is a patch of somewhat hyperplastic liver-cells.

intervening stage between acute yellow atrophy and prolonged subacute cases, while complete recovery is also possible. Indeed, such cases of chronic atrophy may be recognized only when a certain failure of hepatic compensation is induced by some intercurrent condition. As a result, the prognosis of any disease in a case in which there has previously been any prolonged jaundice is necessarily guarded, as the vitality of such an individual with a reduced hepatic reserve is naturally diminished. The disease, in both the acute and subacute forms, almost invariably has an insidious onset unless it supervenes on some other preexisting condition. The whole aspect of the case is different from what is found in ordinary

cirrhosis. The subject may complain of practically no other symptom or sign, except jaundice and, perhaps, some slight diffuse epigastric pain. Gastro-intestinal troubles apparently are not the rule.

As the process becomes more chronic and the regeneration of liver tissue and replacement fibrosis more extensive, the development of ascites is only natural. In several of the more chronic cases which occurred in this institute, ascites has developed in about six months after the onset of the jaundice. Such cases differ from ordinary atrophic cirrhosis only by having none of the toxic appearances or marked enlargement of the spleen as is the rule in cirrhosis.

Acute atrophy, then, bears a certain relationship to all the forms of cirrhosis, and the substance which causes the original liver necrosis may be exactly the same, only varying in intensity and in rapidity of action. Where a poison, derived either from bacteria or from some metabolic product from the intestine, acts on the liver for a short duration and is comparatively mild in toxicity, it causes a destruction of the hepatic tissues toward the periphery of each lobule which may be completely repaired by the remarkable regenerative capacity of the liver-cells; if, however, the destruction be too extensive, it is replaced by connective tissue, and a picture of a monolobular cirrhosis is produced. Such livers are often large, commonly fatty, frequently presenting a smooth surface, and represent what used to be termed "biliary" or "Hanot's" cirrhosis. Should the destructive change be more continuously applied, however, frequently destroying small sections of the liver and, in direct ratio, inducing replacement fibrosis and regenerative activity of the liver-cells, atrophic cirrhosis is produced. In this form, a complete reconstruction of the liver results. The terms "multilobular" or "portal" have been applied to it, but obviously are not correctly descriptive. A continuous or frequently repeated reduction of liver substance, in spite of the great regenerative activity of the liver, eventually reaches a point where insufficiency occurs and the patient succumbs to jaundice. The rearrangement of the liver from necrosis, replacement fibrosis and liver-cell hyperplasia, causes a tortuosity and variation in length and caliber of the blood capillaries which naturally increases the resistance to the portal circulation which may be sufficient to cause ascites. It is, however, easy to see that a slowly progressing liver destruction may continue into an advanced cirrhosis without any jaundice, while only in the latter stages of the disease is ascites manifested, and only after a large amount of liver tissue has been destroyed or some intercurrent disease has developed does jaundice become evident.

In conclusion, one can trace a direct connection between acute atrophy, subacute atrophy and cirrhosis of the liver in all its types, the difference in each depending on the extent and rapidity of accomplishment of the destruction of the liver.

THE DIAGNOSTIC VALUE OF MITOTIC FIGURES IN THE CELLS OF SEROUS EXUDATES*

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Since Quincke's[1] report in 1882, repeated attempts have been made to establish a diagnosis of malignant disease from the character of the cells present in pleuritic or peritoneal exudates. Where bits of tissue are withdrawn by the exploring needle, such a diagnosis may sometimes be made with a fair degree of certainty just as it has been made in the case of tissue obtained in stomach washings, the urine, the feces, etc. The recognition of isolated cancer cells, on the other hand, is extremely uncertain; and in 1900 Widal and Rivaut,[2] after a study of the cells in 600 exudates, concluded that it is difficult to diagnose cancer from such cells, on account of their general resemblance to endothelial cells. In one of the cases to be reported, the presence of many mitotic figures rendered the diagnosis of malignancy almost certain, in the second case their appearance in small numbers strengthened a similar diagnosis, and in the third case they changed a probable diagnosis of sepsis to one of malignancy. A review of the literature shows how few cases have been reported in which large numbers of mitotic figures were found in the cells of serous exudation. We shall therefore report these three cases and review the literature with the object of ascertaining how much reliance may be placed on such findings in establishing a diagnosis of malignant disease.

REPORT OF CASES

CASE I.—*Patient.*—E. T., male, 14 years old, was admitted to the University Hospital March 25, 1910, complaining of swollen abdomen. The family and past history were negative. About Dec. 11, 1909, the patient first noticed sharp pains across the lower abdomen. These recurred at irregular intervals but he did not go to a physician until December 21. In January his abdomen began to swell and he experienced dull pains after eating. Although his appetite remained good he suffered at times from nausea and vomiting. The bowels were loose. Occasionally his feet were slightly swollen. He had a slight cough with a little expectoration. On March 17 six quarts of fluid were removed from his abdomen and on March 24 three quarts more were obtained.

Examination.—The patient was an emaciated, frail boy. In the right clavicular region there was a mass of ten or twelve glands varying from the size of a pea to that of a hickory nut. These were freely movable and not tender. Above

*From the Department of Internal Medicine, University of Michigan.

1. Quincke, H.: Ueber die geformten Bestandtheile von Transsudaten. Deutsch. Arch. f. klin. Med., 1882, xxx, 580.

2. Widal and Rivaut: De l'étude histologique des épanchements sérofibrineux de la plèvre, Compt. rend. Soc. de biol., 1900, lii, 648.

the left clavicle two enlarged glands could be felt, but no other glands were palpable. The lower portion of the chest posteriorly showed dulness with diminished fremitus and breath sounds. The tensely swollen abdomen caused a bulging of the lower ribs; the veins over the sides of the abdomen and chest were dilated.

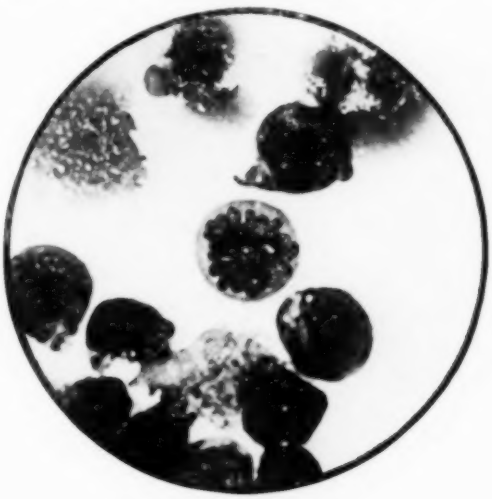

Fig. 1.—Monaster.

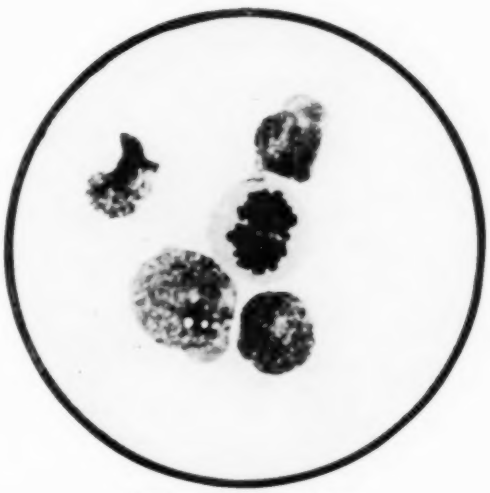

Fig. 2.—Beginning diaster.

Typical signs of fluid in the abdominal cavity were obtained and on palpation an indefinite and deeply situated tumor mass could be felt just above the umbilicus. On March 27, two days after admission, 1,300 c.c. of fluid were removed

from the abdomen. Following the tapping, the tumor could be felt somewhat more distinctly as a transverse mass just to the left of the umbilicus. This was hard and irregular, was firmly fixed and was not tender. Rectal examination showed that it extended into the pelvis in front of the rectum. During his stay

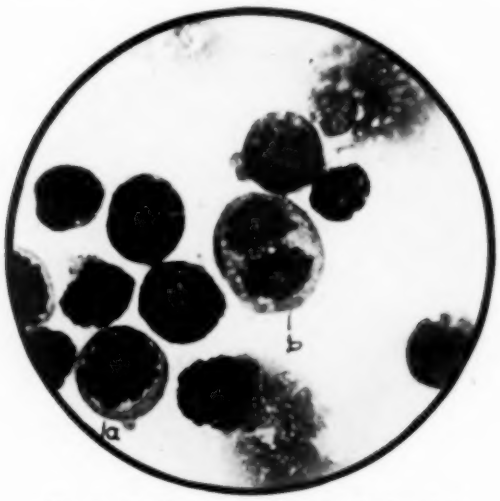

Fig. 3.—Resting tumor-cell (a), diaster (b).

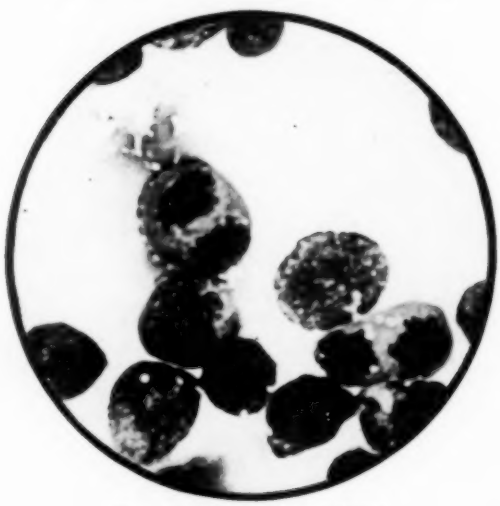

Fig. 4.—Diaster—later stages.

in the hospital his temperature showed a daily fluctuation from about 98 to 100 F. The urinary examination was negative except for the presence of a few granular and hyaline casts and, on one occasion, a blood-cast. The stools showed a positive

occult test for blood with a slightly increased number of muscle fibers. The blood-pressure was normal. The blood examination showed 3,000,000 red cells, 8,000 leukocytes and 55 per cent. hemoglobin. A differential count of the leuko-

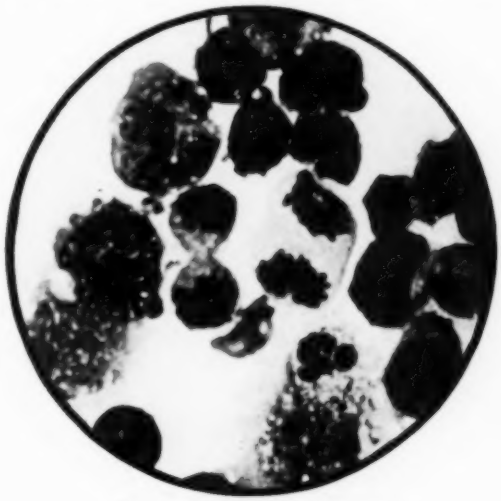

Fig. 5.—Diaster—later stages.

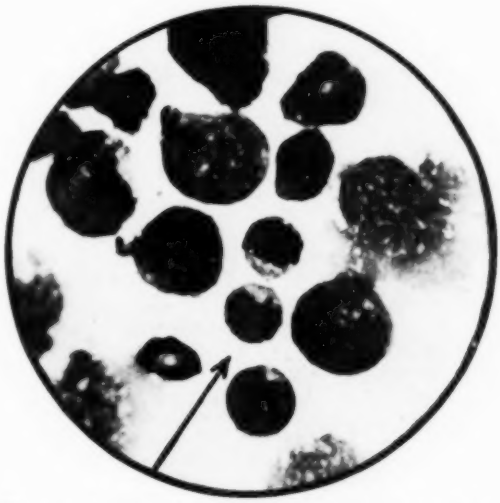

Fig. 6.—Arrow points toward two new tumor-cells.

cytes showed 24.4 per cent. mononuclear cells, 71.4 per cent. polynuclear, 0.7 per cent. eosinophilic mononuclears and 3.5 per cent. degenerates. The fluid obtained from the peritoneal cavity showed the following characteristics: specific

gravity, 1.010; large amounts of albumin (one half volume by heat and nitric acid test; 15 gm. per liter by Esbach); very heavy test for nucleo-albumin; tests for mucin, sugar and bile negative. It contained 17,320 white cells per c.mm. A differential count of these showed 37 per cent. typical small lymphocytes, 51 per cent. atypical mononuclear cells and 12 per cent. polynuclear. Eight red cells were noted in counting 200 white cells. Every field of prepared films showed tumor cells in both resting and division stages. The former could be told from the lymphocytes: (1) by their size, they being from 16 to 24 microns in diameter; (2) from the nucleus, which did not stain as heavily and gave the appearance of being fissured or slightly lobulated; (3) the protoplasm was increased in amount over that of the lymphocytes and most frequently showed small areas of vacuolization. Of the division figures, the monasters (Fig. 1) were the most plentiful, but there were all stages passing from same down through the equatorial plate arrangement to the typical diaster (Figs. 2 and 3). Cells showing beginning constriction of the protoplasm (Figs. 4 and 5), as well as new tumor cells ready to separate (Fig. 6), were fairly abundant. The figures here pictured were all taken from the preceding case; about one cell in twenty-five showed some form of division.

Course.—The patient rapidly failed after coming into the hospital and died on April 1, of exhaustion. At first he was suspected to have a peritoneal tuberculosis but the absence of a Pirquet reaction, the failure to find tubercle bacilli in the peritoneal fluid and in the stools, and the large number of mitotic figures in the cells of the ascitic fluid changed the clinical diagnosis to a neoplasm involving the peritoneal cavity.

Pathology.—At necropsy, performed by Dr. Warthin, on April 1, 1910, the whole abdomen was found to be filled with a soft, nodular mass which proved to consist mainly of tumor of the omentum. The coils of the intestines were covered with a fibrinous exudate. Tumor nodules were present in the mesentery, intestines, peritoneum, and retroperitoneal glands and tissues. The diaphragm and the parietal pleura were studded with tumor masses. Nodules present on the lower surface of the right lung had apparently extended to it from the diseased diaphragm. The tumor had also involved the bronchial glands, the spleen, the kidneys, the liver and the bladder-wall. Microscopically it proved to be a lymphosarcoma. The origin of the tumor could not be determined.

Case 2.—*Patient.*—W. B., aged 32, entered the University Hospital on Feb. 21, 1910, complaining of abdominal enlargement. The family and past history were negative. The present trouble began six weeks before admission, when the patient first noticed that his abdomen was becoming swollen. On the following day he was suddenly taken with sharp, paroxysmal pains in the left lower abdomen, which radiated to the right side. Following this the abdomen grew rapidly in size and, although the severe pains abated, he had distress after eating; became very weak and dyspneic, and lost about 20 pounds in weight.

Examination.—The patient was a moderately emaciated man. The abdomen was very much distended, bulging somewhat more to the left than to the right. On account of the tension, palpation was difficult but in the left flank a hard mass could be indistinctly felt. February 22, the abdomen was tapped and 6 liters of a brownish, slightly turbid fluid were removed. Following this a nodular mass could be felt, extending from somewhat above the umbilicus down to Poupart's ligament on either side. This was hard, rather nodular, and but slightly movable. Rectal examination showed that the mass extended into the pelvis in front of the rectum.

Course.—The fluid collected rather rapidly after the tapping and respirations became increasingly more difficult. On March 2 the patient was again tapped and 7,700 c.c. of yellowish-brown fluid obtained. Following this tapping, the fluid did not re-collect so rapidly but the patient gradually became weaker, vomited considerably and died on March 14.

Numerous blood-counts showed a normal number of red blood-corpuscles and a normal percentage of hemoglobin. The leukocytes were moderately increased, ranging from 10,500 to 15,000. No abnormalities in the appearance of a stained smear were noted. The urine was negative; the stools showed heavy tests for occult blood. The injection of 5 mg. of tuberculin produced no reaction. An examination of the fluid recovered at the second tapping showed a specific gravity of 1.018 and large amounts of albumin, so that the tube boiled solid. The fluid contained 1,400 white cells and 240,000 red cells per c.mm. The differential count of the whites gave 61 per cent. lymphocytes, 7 per cent. polynuclears, and 32 per cent. large mononuclear cells. A small number of mitotic figures were found. A clinical diagnosis was made of malignant tumor involving the omentum.

Pathology.—At the necropsy, performed by Dr. Warthin, March 16, 1910, the omentum was found greatly thickened and nodular, forming a thick apron reaching to the pelvis. Fifteen hundred c.c. of fluid of an opalescent, sticky character were found in the left pleural cavity. A smaller amount of fluid was present on the right side. The parietal pleura showed numerous minute tumor granules, with some nodules on the visceral pleura. The peritoneum was thickened and edematous and was covered with a fibrinous exudate. At the pylorus was found an irregular ulcer, 2½ inches in diameter, with slightly elevated borders. Opposite the ulcer there was a nodular mass of tumor tissue. The smaller intestines were encased in a layer made up of tumor tissue and fibrin. Lymphatics in the lesser curvature of the stomach were enlarged and nodular. Several tumor nodules were present in the liver. On section, the tumor proved to be a colloid carcinoma; in places of the adeno type, in other places rather scirrhus. The cancer showed marked mucoid degeneration.

CASE 3.—*Patient.*—Miss R., seen by Dr. Hewlett in consultation with Dr. Gates of Ann Arbor, on August 22, 1911, complaining of weakness, also emaciation and fever. Family history negative. Past history negative up to about one year ago at which time a multilocular cyst of the ovary was removed by Dr. Darling. Subsequently she had a stitch abscess but recovery was otherwise perfect. About July 4, 1911, she noticed a pain in the left foot, and a week or so later a pain in the right side. She had lost weight and strength almost continually since that time. She had noticed no chills or sweats but her temperature for the past few days had ranged between 100 and 101 F. She had had a succession of reddish spots appear under the skin which were painless, not tender, and gradually faded. She had coughed considerably especially when she raised mucus.

Examination.—Patient appeared seriously ill. The skin was sallow and there was some dyspnea. At the base of the left chest behind there were numerous crackling râles. At the right base there were signs of fluid extending to the sixth or seventh spine behind, well up into the axilla, and to about the fourth intercostal space in front. Beneath the skin in various parts of the body were a number of spots which were reddish, slightly elevated and from 2 to 3 cm. in diameter. The older ones faded to a yellowish color. The blood showed no marked anemia. There were 17,000 leukocytes. The stomach analyses had shown little or no free hydrochloric acid. The sputum was negative for tubercle bacilli on several examinations. The fluid aspirated from the right chest and was bloody in appearance. Smears of the centrifugalized material showed a great many red cells, most of which are either broken or cremated. The polynuclears have a predominance over the mononuclears, they making up 82 per cent. of the differential blood-count. In addition to these cells already mentioned are large numbers of balls of cells, similar to those described and pictured by Quincke. The nuclei in these cells stain poorly and the protoplasm of many show fatty degeneration. They vary in size from 30 to 50 microns in diameter and some of the cellular groups have a diameter of 100 microns. With the Wright stain the nuclei in these groups are placed at the periphery while the center stains rather palely. In both the single cells and cell masses are found division figures. Most of these are in the monaster or beginning diaster stage.

Diagnosis.—Previous to the aspiration of the fluid from the right chest, and under the impression that the ovarian tumor had been benign, a tentative diagnosis of sepsis was made based on the fever, leukocytosis, effusion and subcutaneous spots. Later it seemed much more probable, however, that we were dealing with a malignant disease of the pleural cavity, in view of the character of the exudate and subsequent examination of sections of the tumor. The latter were examined by Dr. Warthin, who reported a papilliferous cystadenoma with layers of necrosis and areas of active cell proliferation almost solid. He expressed the opinion that the tumor was malignant.

Course.—The patient failed rapidly and died Aug. 27, 1911. No autopsy was obtained.

REVIEW OF LITERATURE

To ascertain the diagnostic value of mitotic figures in serous exudates one must consider their frequency in malignant as well as in non-malignant conditions. Reider[3] first described such figures in an exudate due to malignant new growth. In his case both ascitic and pleural fluids showed many division figures of mitotic as well as of amitotic nature, and at post mortem a sarcoma (carcinoma?), probably beginning in the ovary, was found. In 1897 Dock[4] reported a case of carcinoma of the stomach undergoing colloid change, in which many cells of the ascitic fluid showed mitotic figures. In the same article he mentions a pleuritic exudate secondary to carcinoma of the breast where a few mitoses could be found. In the same year Warthin[5] reported a spindle-celled sarcoma invading the pleural cavity. The pleuritic exudate showed typical small spindle cells, with numerous division figures. Turton,[6] in 1905, mentioned a case in which the fluid from the right side of the chest showed "large sarcoma cells with mitotic nuclei," the diagnosis being confirmed at autopsy. Mitotic figures in the spinal fluid have been described by Widal and Abrami,[7] and by Facchini[8] in cases of sarcoma involving the meninges. Marini and Fiorini[9] reported four cases of carcinoma with effusions and claimed to have found division figures in each. Their microphotographs, however, are not convincing. Their figures showed

3. Reider, G.: Zur Diagnose der "Neubildung" bei klinische mikroskopischen Untersuchungen von Transsudaten, Deutsch. Arch. f. klin. Med., 1895, liv, 544.

4. Dock, G.: Cancer of Stomach in Early Life and the Value of Cells in Effusions in the Diagnosis of Cancer of the Serous Membrane, Am. Jour. Med. Sc., 1897, cxiii, 655.

5. Warthin, A. S.: The Diagnosis of Primary Sarcoma of the Pleura from the Cells Found in the Pleuritic Exudate, Med. News, 1897, lxxi, 489.

6. Turton, E.: The Cytodiagnosis of Pleural and Cerebrospinal Fluids, Practitioner, London, 1905, lxxiv, 497.

7. Widal, F., and Abrami, P.: Cytodiagnostic du cancer des centres nerveux. Présence de cellules néoplastiques dans le liquide céphalo-rachidien endocardite végetante cancéreuse, Rev. Neurol., 1909, xvii, 75.

8. Facchini, G.: Un caso di sarcomatosi diffusa metastatica della pia meninge cerebrale e spinale con caratteristico reperto citodiagnostica del liquido cefalo rachidiano, Policlinico, Rome, 1908, xv, 977.

9. Marini, D. G., and Fiorini, M.: Valore dell' esame istologico dei liquidi ascitici nella diagnosi della neoplacie peritoneali, Riforma Med., 1908, xxiv, 1.

cells with several separate nuclear masses but without mitotic skeins. Such cells are found in a great many effusions other than malignant ones. In spite of a careful search of the literature, the above were the only cases discovered in which exudates due to malignant disease showed free cells undergoing mitotic division. It is probable, of course, that others have been observed and that a few reports have been overlooked. Raubitschek[10] has expressed the opinion that division figures, typical or atypical, indicate the neoplastic nature of the exudate with a probability bordering on certainty.

On the other hand, numerous effusions complicating malignant disease have been reported in which division figures were not described. Seven such were reported by Ross,[11] six by Schlesinger,[12] five by Barjon and Cade,[13] two by Gwyn,[14] three by Miller,[15] one by Vickery, Wright and Richardson,[16] one by Miller and Wynn,[17] two by Beneke,[18] and one by Gulland.[19] Labbé, DeLillie and Aguinet[20] report a case of sarcoma of the pleura in which they recognized sarcoma cells but were unable to find division figures. Nattau and Larrier[21] also recognized cancer cells in cases of cancerous pleurisy but were unable to find divisions. In two cases of malignancy during the past year we were unable to find division figures. In many of the above cases division figures were expressly looked for while in others no mention was made of their absence. Malignant disease may cause exudates by a mechanical obstruction of the veins or lymphatics or by exciting a low-grade inflammation. In many of these cases, how-

10. Raubitschek, H.: Die cytologie der Ex- und Transsudate, Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1906, ix, 337.

11. Ross, E. A.: A Study of Cytodiagnosis with Especial Reference to Its Application in Clinical Medicine, Tr. Path. Soc. London, 1906, lvii, 361.

12. Schlesinger: Ueber das Auftreten von Mononucleose in Pleura exudation bei Lungen- und Pleuratumoren, Wien. Gesellsch. f. inn. Med. u. Kinderh., 1909, xii, 960.

13. Barjon, F., and Cadé, A.: Eosinophilie pleurale, Arch. gén. de méd., 1903, excii, 1859.

14. Gwyn, N.: Carcinoma of Abdominal Cavity. Puncture of Intestine During Paracentesis Abdominis, Am. Jour. Med. Sc., 1904, cxxvii, 592.

15. Miller, J.: Transudates and Exudates with Report on Seventy-Five Fluids, Am. Med., 1904, viii, 835.

16. Vickery, H. F., and Richardson, O.: Malignant Disease of Pleura, Boston Med. and Surg. Jour., 1907, clvii, 824.

17. Miller, J., and Wynn, W. H.: A Malignant Tumor Arising from Endothelium of the Peritoneum and Producing a Mucoid Ascitic Fluid, Jour. Path. and Bacteriol., 1908, xii, 267.

18. Beneke: Ueber freies Wachstum metastatischer Geschwulstelemente in serösen Höhlen, Arch. f. klin. Med., 1899, lxiv, 237.

19. Guilland, G. L.: Cytodiagnosis of Pleural Effusions, Scot. Med. and Surg. Jour., 1902, x, 490.

20. Labbé, Delillie and Aguinet: Cytodiagnostic de la pleurésie sarcomateuse, Bull. Soc. d'anat. de Paris, 1902, Serie VI, iv, 507.

21. Nattau and Larrier: Cytologie des pleurésies cancereuses, Compt. rend. Soc. de biol., 1905, p. 709.

ever, tumor tissue involved the serous membranes and not a few authors regarded the cells present in the effusion as tumor cells. We have already mentioned the difficulty of recognizing free-growing tumor-cells in serous exudates. In Beneke's third case, however, the cells showed pigment similar to that in the parent melanosarcoma and there was little doubt about their nature. In the great majority of cases, therefore, mitotic figures have not been found in the exudates accompanying malignant disease. Occasionally, however, they occur in such number as to form the most striking feature of the cell-count.

There remains for consideration the occurrence of mitotic figures in the cells of exudates due to other causes than malignancy. Personal experience as well as a review of the literature indicate that mitotic figures are extremely rare in such exudates. Only two instances have been encountered in literature. One was reported by Dock in a pleurisy following the removal of a diseased appendix. This was probably of an infectious character as was shown by the large number of pus-cells and the presence of streptococci. The other was reported by Ross, in a patient whose clinical history suggested tuberculosis and who was in satisfactory condition eleven months after the tapping. In Dock's case the number of mitotic figures was not very great; in Ross' they were said to be numerous, and it is to be regretted that more data concerning this case are not available. The extreme rarity of mitotic figures in non-malignant effusions is now well established, for the active interest in cytodiagnosis during the past few years would certainly have brought to light more cases had they existed. It is probable, as Dock has said, that "the difference between malignant and non-malignant exudates in this regard is of degree rather than of kind." Where great numbers of figures are found, the diagnosis of malignancy is almost certain while, where few are present, the diagnosis is suggested but not certain.

The cases showing numerous, actively-dividing cells, free in the fluid have occurred most frequently in cases of sarcoma. In Dock's case, however, the diagnosis was colloid carcinoma. Beneke has described a case of carcinoma involving the pleural cavity in which balls of free-growing, unattached tumor-tissue were found in the pleural cavity. The cells in these balls frequently showed mitotic figures. In two cases of sarcoma, on the other hand, he found free, individual cells which he regarded as tumor-cells. He is inclined to explain the difference by assuming that in carcinoma new stroma was formed which held the cells together, while in sarcoma this was lacking and the cells appeared free in the fluid. When many mitotic figures are present the tumor-cells are proliferating actively in the body-fluids. The condition may be of some biological interest in connection with the fact that tumor-cells have recently been cultivated outside of the body. Their free growth in a serous exudate

MALIGNANT EFFUSIONS WITH MITOTIC FIGURES

Author	Date	Age Yrs.	Character of Tumor	Site of Tumor	Differential Count, Etc.
Rieder	1895	..	Sarcoma (carcinoma ?)	Prim. ovary; sec. peritoneum, pleura, etc.	Cells vary in size and shape; great variation in the nuclei; many mitotic figures.
Dock	1897	20	Cancer	Prim. stomach; sec. peritoneum.	Many mitoses so that every contains one or more.
	1897	50	Carcinoma	Prim. breast; sec. pleura.....	Excessive red-cells and lymphocytes; many mononuclear and few endothelial cells; very few showed mitoses—two to two in each preparation.
Warthin	1897	47	Sarcoma	Prim. pleura	Many typical spindle cells, singly and in groups; numerous mitoses of symmetrical character.
Turton	1905	23	Sarcoma	Pleura	"Large sarcoma cells with mitotic nuclei."
Widal and Abrami..	1908	47	Carcinoma	Prim. stomach; sec. internal capsule.	Cells gave glycogenic reaction.
Facchini	1909	..	Sarcoma	Prim. —; sec. meninges.....	Neoplastic cells with mitosis.
Warren	1911	14	Lymphosarcoma	Prim. mesentery and intestines; sec. peritoneal cavity.	37 per cent. lymphocytes, 51 per cent. atypical mononuclears, 12 per cent. polynuclears; very numerous mitoses.
	1911	32	Colloid carcinoma....	Prim. stomach; sec. peritoneum.	61 per cent. lymphocytes, 7 per cent. polynuclears, 32 per cent. large mononuclears; many red-cells; very few mitoses.
	1911	48	Papilliferous cystadenoma	Prim. ovary; supposed sec. pleura	80 per cent. polys., great many red cells, many balls of cells, numerous mitoses.

would seem to indicate that the body defenses have practically succumbed to the neoplasm.

CONCLUSIONS

1. Very many cells undergoing mitotic division in serous exudates are almost diagnostic of malignant disease.

2. This occurs more often in sarcoma than in carcinoma.

3. A small number of mitotic figures is suggestive of malignant disease but is of no certain value in diagnosis.

4. In the majority of the exudates associated with malignant disease no division figures are seen.

I wish to thank Dr. A. M. Barrett for the microphotographs which he so willingly made for me.

PERCUSSION SIGNS OF PERSISTENT OR ENLARGED THYMUS *

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Although we know very little about the functions of the thymus, it has certain clinical associations which make it important, and closer observation may enlarge our knowledge of its relation to disease.

The gland occupies a position high in the superior mediastinum, lies close to the sternum and it is not covered by the lungs. Ordinarily the lobes are unequal, the left being the larger and longer, often extending as low as the fourth rib in infants. The gland is attached by one or two suspensory or thyrothymal ligaments to the lower poles of the corresponding thyroid lobes. Otherwise the thymus is but slightly bound to the surrounding tissues and is free to move in the direction of the long axis of the sternum. If it is borne in mind that the thyroid gland is in turn connected to the hyoid bone and from this to the mandible by more or less continuous ligaments and muscles, it is seen that a ligamentous chain extends from the anterior part of the lower jaw obliquely downward and backward to the thymus.

This connection is of interest in explaining the mechanics of the movable thymus dulness described below; for in retraction of the head, more tension is brought to bear on the structures anterior in the neck than those lying close to the vertebral column, and these structures move through a greater arc.

In the normal atrophic state of the adult thymus, the small amount of gland substance and areolar tissue is too thin to give any appreciable dulness on percussion over the manubrium, or just to the left of the sternal margin. But if, for any reason, the gland has not atrophied or has become enlarged, then there is a dulness easily determined on medium percussion over the manubrium and in the first and second left interspaces, more rarely in the third interspace. In many cases, also, this dulness is perceptible to the right of the sternum in the first interspace; less frequently in the second.

The differentiation of dulness in the mediastinum due to thymus enlargement from other masses in this region will depend on several factors.

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*Read at the twenty-sixth annual meeting of the Association of American Physicians, Atlantic City, May 9-11, 1911.

1. The thymus is higher and more superficial than the mediastinal lymph-glands usually involved in tuberculous or other mediastinitis, or which may be the seat of primary or metastatic tumors. These lymphatics lie deep, near the hilum of the lung, and when diseased, are usually more or less fixed by adhesions to the surrounding tissues. It is further to be observed that thoracic aneurysms, tumors, or inflammatory masses of the mediastinum are practically fixed in position and no considerable change in percussion is made out, when the head is retracted.

2. Thymus dulness is almost constantly much more marked on the left of sternum than on the right.

3. Thymus dulness can be made to shift by the following maneuver, viz.: The patient sits up; the back is supported by the nurse or assistant, if necessary. The chin is depressed toward the sternum. The dulness is outlined behind the manubrium and in the interspaces, then the head is retracted as far as possible toward the mid-line of the back and, on repeating the percussion, the lower border of dulness will be seen to have shifted upward, often as much as an interspace or more. On again depressing the chin, the dulness assumes its former position. In recognizing minor degrees of movement, it is advisable to keep the pleximeter fingers constantly in place, avoiding the slight movement of the skin by first pushing the skin up toward the neck before the retraction of the head puts it in tension.

Another point which may be noted here is the fact that in some cases of persistent or enlarged thymus, there may be no dulness in the first interspace, but only in the second and below it. In such instances, a shift in both upper and lower borders of dulness may be made out.

The material on which these deductions are based was derived from an orphan asylum for colored girls and from the wards of the Johns Hopkins Hospital and the City Hospital.

In the orphan asylum, sixty-six girls were examined during an epidemic of measles. Of these, fourteen had the disease or were convalescent. In age they were between 5 and 18 years, thirty-seven of them between 10 and 14 years. Of the sixty-six children, thirty-five showed positive signs of persistent or enlarged thymus. This number included twelve of the measles cases. All but three of the positive cases showed general lymphadenitis of varying grades; many had also hypertrophied tonsils.

Of the hospital patients, fourteen in number, nine were between 8 and 18 years, and five between 22 and 47 years. Of the fourteen patients, only five were colored. The children were nearly all sick with acute infections, including typhoid, pneumonia, pleuritis, diphtheria, etc. Of the adults, two had exophthalmic goiter and two diphtheria, though it is to be observed that these last have still the same signs of enlarged thymus, a year or more after the diphtheria. The extent of dulness varied from 2 to 7 cm. from the midsternal line, the average being about 2.5 to 3 cm.

Only two patients could be examined with Röntgen ray. Both had very large glands and showed a shifting shadow in the thymus region to left of the manubrium.

One case of the series came to autopsy, when the percussion findings were amply confirmed by the presence of a gland measuring 9 cm. by 8 cm. by 2 cm.

In conclusion, it may be remarked that lymphatic hyperplasia seems to be more common in the black race, which may explain the high percentage of positive findings in the orphan asylum children.

This method is put forward tentatively and for criticism, as it has not been noted in the literature on physical diagnosis.

Special thanks are due to Drs. C. R. Austrian and W. L. Estes for assistance in the study of the orphan asylum cases.

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NITROGEN AND FAT METABOLISM AND OTHER FUNCTIONAL TESTS IN A CASE OF CHRONIC PANCREATITIS *

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A case of chronic pancreatic insufficiency without diabetes will be reported here, with special reference to the metabolism of nitrogen and fat. A discussion of other functional tests of the pancreas is included. The patient was one of Dr. L. F. Barker's in the medical clinic of the Johns Hopkins Hospital. This report falls under three general heads: (1) Clinical Course; (2) Metabolism Studies; (3) Other Functional Tests.

CLINICAL COURSE

Patient.—Med. No. 24917. W. P. R., aged 34, attorney. Admitted Nov. 20, 1909, complaining of indigestion and diarrhea. The following history was obtained at that time.

Family History.—Negative. A long-lived healthy family.

Personal History.—He had had the usual diseases of childhood, and diarrhea of varying severity from the age of 3 to 13 years, malaria at 22, "eczema" with painful pruritus of arms, legs and back, from the age of 25 to 30 years. There were occasional attacks of sharp pain in abdomen during greater part of life. Alcoholic and venereal history were negative.

Present Illness.—Began September, 1908, with nocturnal attacks of severe pain in epigastrium. Occurrence every three or four nights, gradually increasing in frequency until occurring every night. Entered a hospital in North Carolina Nov. 19, 1908, with diagnosis of cholecystitis.

Operation.—Nov. 24, 1908. Pus was found in gall-bladder and about 75 gall-stones were removed ranging in size from a wheat grain to a pea. A few were found in the hepatic duct and one in the common duct. No bile in stools at time of operation. Bile appeared first on the third day after operation. Left hospital after one month.

Jaundice, present previous to operation, persisted until March, 1909. A skin rash on head, arms, legs and lower abdomen in the form of red concentric rings appeared with pruritus at close of January, 1909; duration three weeks.

Patient has not had a formed stool since operation. Stools are said to have been for the most part pasty, yellow or clay-colored. Feb. 15, 1909, diarrhea began, with one to five stools a day, continuing to the present time. Marked loss of weight.

Patient was in a sanatorium from March 25 to May 15, 1909, with temporary anasarca. Since then unable to work except a small amount in September, 1909. Has had no abdominal pain since operation and gives no history of excessive salivation.

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*From the Chemical Division of the Medical Clinic of the Johns Hopkins Hospital.

Physical Examination.—A very much emaciated man, muscles markedly wasted. Extreme pallor of mucous membranes. Mind clear and active. Eyes, ears, throat, lungs and heart normal. Pulse, small volume, regular in force and rhythm; artery wall slightly sclerotic. Abdomen scaphoid, walls thin. Large operative scar in right upper quadrant. Liver edge slightly lower than normal. Spleen not palpable. Rectal examination negative. Reflexes normal.

Urine.—Amber or orange color, slightly cloudy, specific gravity 1008-1020. Acid. No sediment. Sugar negative. Albumin 0.25 gm. (Tsuchiya reagent). Microscopic examination negative. Bile +. Urobilin +. Indican negative. Cammidge reaction: No crystals were obtained from 50 c.c. From 4 liters, large yellow sheaves soluble in dilute sulphuric acid were obtained with melting-point 130 F.

Stools.—Macroscopic. Nov. 20, copious semi-solid, very fatty throughout, appearing like butter and giving the odor of butyric acid. Large quantities of undigested particles of meat, potatoes, etc. After November 22, dark brown, thick fluid, steatorrhea diminished or absent, still many undigested food particles. Stool sometimes showed oily layer over surface. Sublimate test for bile: positive for urobilin, on one occasion showed bilirubin also. Occult blood test negative. Gross' casein test showed presence of trypsin. Schmidt's nuclei test showed few nuclei intact.

Microscopic: Neutral fat in amounts varying with macroscopic appearance. Large and small droplets staining red with Sudan III. Fatty acid crystals. Large numbers of striated muscle fibers, some showing nuclei intact. No parasites. No stones of any sort.

Blood.—Fresh smears normal. R. B. C., 3,056,000. Later 4,000,000. W. B. C., 7,000. Hemoglobin (Sahli) 70 to 79 per cent.

Stomach Contents.—Forty-five minutes after a Dock test breakfast (1 shredded wheat biscuit with 400 c.c. of water), 40 c.c. of fluid were recovered containing no free hydrochloric acid. Total acidity 4.0 "acidity per cent."

Patient's weight 100½ pounds.

Subsequent Course.—Little change in condition during two weeks of metabolism studies. Weight varied as follows: November 28, 101 pounds; December 5, 97 pounds; December 10, 98½ pounds; December 13, 101 pounds; December 18, 103 pounds.

December 11, marked improvement began on light diet with pancreatin rhenania gr. iii p. c. and $CaCO_3$ gr. iii p. c. Daily examination of urine, while in hospital, gave negative Fehling's tests without exception. Left hospital Dec. 27, 1909, weighing 120 pounds, including wearing apparel.

March 1, 1910: Patient began to have formed stools. April 1910; weighed 147 pounds. May 10, 1910; examination by Dr. Barker showed condition much improved, muscles growing rapidly. Patient works seven hours a day. Is taking 6 gr. pancreatin (r) with $CaCO_3$ daily. August, 1910, discontinued all medication. Jan. 2, 1911, at work and quite well. Weight 158 pounds. Examination of one day's feces received on Jan. 27, 1911; rather large amount, color varying from brown to yellow; consistency, thick, pasty throughout; no lumps. Microscopic: A fairly large number of muscle fibers with striations intact. No nuclei seen. Numerous small and large fat globules (staining red with Sudan III). Urobilin abundant. Trypsin: Gross' test showed complete digestion of casein within fifteen hours.

April 26, 1911. Patient writes that he is doing an average amount of work and is in every way normal, except for some nervous excitability and an occasional slight attack of diarrhea. He weighs over 150 pounds, and has taken no medicine of any kind since last August, but still eats with regularity and care.

The cardinal symptoms of pancreatic insufficiency are diabetes, steatorrhea and azotorrhea. The last two alone are present in this case, indicating impairment of the external secretion only.

Chronic pancreatitis with indications so characteristic is relatively infrequent for several reasons (Oser[1]):

1. For each digestive function of the pancreas, ferments in one or more collateral organs exist (e. g., lipase in the gastric juice, putrefactive enzymes in the intestine, proteolytic ferments in the gastric juice and succus entericus).

2. Santorini's duct may compensate entirely for the obliteration of the duct of Wirsung.

3. A large part of the pancreas being functionally deficient, a small remnant will often suffice for the work required.

4. Pancreatic disease is frequently combined with disease of neighboring organs.

It has been suggested further, by A. Schmidt and others, that in simple obstruction the ferments may reach the intestine by way of the circulation. (Rosenberg explained the condition of his dog during the first month in this way. See Table 2.)

Before a diagnosis of chronic pancreatitis can be established, two other conditions must be considered in which azotorrhea and steatorrhea may occur: i. e., biliary obstruction and impaired intestinal absorption. The first, although it had played an important part in this case, was excluded by the absence of jaundice at the time and for the previous nine months. The character of the stools was distinctly pancreatic rather than biliary. Such conditions as amyloid disease, atrophy of the intestinal mucosa, tabes mesenterica and tuberculous peritonitis were excluded by lack of confirmatory evidence, history of cholecystitis and most conclusively by improvement under organotherapy. Accelerated peristalsis and intestinal catarrh can cause marked protein and fat losses.

METABOLISM STUDIES

Literature: Clinical and experimental cases of pancreatic insufficiency have been compiled in Tables 1 and 2, respectively. They are selected chiefly with reference to studies in which the intake and output of protein and fat have been carefully compared. The later ones, as in this case, illustrate the effect of various therapeutic measures; some older cases are included which exhibit features of special interest, although furnishing no quantitative data.

Those of Kuntzman and Richard Bright were the first, in which the correlation of fatty stools with pancreatic disease was established. Fles first noted the presence of unabsorbed protein in large amounts, as well as fat, and was able to vary these conditions at will by the feeding of fresh pancreas.

The first quantitative studies were directed toward estimating the proportion of fat contained in the feces. This has been done in many cases. Müller gives 21 per cent. as a normal figure. Brugsch has con-

cluded that a fat content of over 30 per cent. of the dry weight of the feces suggests impairment in absorption. This can attain to 80 per cent. in icterus and the average for pancreatic disease is 60 per cent. It may be much lower when azotorrhea is marked. The point is one of comparatively slight value, as Müller states in his classical "Untersuchungen über Icterus."

Here he insists that the percentage of fat cleavage is far more significant. In his three cases, the average proportion of total fat found in split form is 39 per cent.; 84.3 per cent. is the figure which he gives as normal. Katz holds that a cleavage of less than 70 per cent. indicates pancreatic impairment. Fitz,[23] in a compilation of ten cases of undoubted pancreatitis in which the fat cleavage was noted, finds variations all the way from 8.4 to 82.5 per cent. He concludes, that in general the view of Müller is borne out, that fat-splitting is diminished. In nine cases of Alexander and Ury, the split fat varied from 9 to 86 per cent. Brugsch, on the contrary, believes that in acute and chronic pancreatic disease, the fat splitting is practically uninfluenced. The soaps may be diminished in amount on account of decreased alkalinity.

The absorption of nitrogen and fat in pancreatic insufficiency was first studied quantitatively in the well-known work of Abelmann. This was done on Minkowski's dogs, immediately after the latter with von Mering had demonstrated the relation of pancreatectomy to diabetes.

Abelmann obtained a higher degree of absorption when fat was fed in emulsified form (especially as in milk); nitrogen and fat absorption were both improved by the feeding of pigs' pancreas or "pancreatinum."

Brugsch found, in contradiction to Abelmann, that fats in non-emulsified form are not wholly unabsorbable for totally pancreatectomized dogs. He further believes that, in the human intestine, milk is no better absorbed in pancreatic insufficiency than non-emulsified fats.

In thirteen of the clinical cases since that time, the average absorption of fat has been 45.2 per cent. of the intake (where the effects of organotherapy are excluded). The figures, however, have varied widely. In one of Brugsch's cases with complete biliary and pancreatic obstruction, 11 per cent. only was absorbed, while in the present case, on a low diet with fat given chiefly as milk, 95.7 per cent. was absorbed without therapy. There is good evidence that fat absorption fares worse when pancreatic disease is complicated with icterus.

In regard to nitrogen absorption, we have a more constant finding in the various cases reported. It is rarely found below 50 per cent. or above 80 per cent. in chronic pancreatitis. The average of eleven cases in Table 1 (therapeutic effects excluded) is 63.2 per cent. Brugsch's 75 to 80 per cent. probably places it too high. He regards the nitrogen disturbance as quite secondary in importance to that of fat. Weintraud, on the other hand, probably came nearer the truth in attributing to the

TABLE 1.—CLINICAL PANCREATIC DISEASE

Author	Date	Diagnosis	Glycosuria	Jaundice	Per Cent. N. Absorption	Per Cent. Fat Absorption	
Kuntzmann[2] ..	1820	Induration of pancreas; duct obliterated.	0	+	....	Low.	First correlation of fatty stools with pancreas.
Bright[3]	1833	Carcinoma of pancreas.....	+	+	....	Low.	Seven pancreatic cases in all; one other had fatty stools.
		Carcinoma of pancreas.....	0	0	....	Low.	
Fles[2]	1864	Chronic pancreatitis	+	..	Low.	Low.	First noted azotorrhea; condition of stools varied at will by feeding calves' pancreas.
Ziehl[2]	1883	Carcinoma of pancreas; duct closed.	0	0	....	Low.	50 per cent. of dried stool-fat.
Demme[2]	1884	Congenital syphilis pancreas and liver.	0	+	....	Low.	64-73 per cent. fat.
Müller[4]	1887	Obstructed duct	0	+	Low.	Low.	39 per cent. of fat split in average of three cases; 84.3 per cent. given as normal amount split.
		Cyst of pancreas.....	0	0	Low.	Low.	
		Pancreatic calculus with atrophy.	+	0	Low.	Low.	
Le Nobel[5].....	1888	Chronic pancreatitis	+	0	....	Low.	No fatty acid or indican; thought maltosuria important.
Von Noorden[6] .	1890	Necrosis of pancreas.....	..	..	....	Low.	Feces obtained at autopsy. 29.5 per cent. of fat split.
		Carcinoma of pancreas.....	..	..	....	Low.	8.4 per cent. of fat split.
Hirschfeld[7] ...	1891	Probable pancreatitis (6 cases)	+	0 +	68.2	65.2	Icterus in one case.
Oser[1]	1893	Chronic pancreatitis	0	+	....	Low.	46 per cent. of dried stool-fat.
Weintraud[2] ...	1898	Chronic pancreatitis	.. ..	.. ..	54—58	78—75	Says N disturbance more important than fat in pancreatic disease.
Deucher[8]	1898	Carcinoma pancreas	+	0	70.4	17.1	Average lecithin output 9.3 gm. in three cases. 80 per cent. of fat split.
		Carcinoma pancreas	0	+	81.0	47.4	62 per cent. of fat split.
Katz[22]	1899	Indurated pancreas with hemorrhage and necroses.	..	+	....	Low.	13.93 per cent. of fat split.
Northrup and Herter[9].....	1899	Carcinoma pancreas	0	+	....	Low.	82.5 per cent. of fat split.

Norrup and Herter[9]	1899	Carcinoma pancreas	0	+	....	Low.	82.5 per cent. of fat split.
Masuyama and Schild[10]	1899	Chronic pancreatitis (1 case).	+	0	....	37	Without therapy.
						64	Fresh pancreas fed.
						45	Pancreatic juice fed.
Salomon[11]	1902	Chronic pancreatitis (1 case).	+	0	30	48	Without therapy.
					78	80	Pancreas fed.
					13	47	Without therapy.
					75	83	Pancreatin rhenania.
					32	62	Without therapy.
					78	79	Pancreon.
Telcky[12]	1902	Fibrous pancreatitis	+	+	....	Low.	51.42 per cent. fat split.
Kinnicutt[13]	1902	Pancreatic calculi in stools	0	0	....	Low.	57 per cent. of fat split.
Glaessner and Sigel[14]	1904	Chronic pancreatitis (1 case).	0	0	52—55	38—44	Without therapy.
					56.7	68.5	Pancreatin rhenania.
					58	58.7	Pancreon + alkali.
					62	69.8	Pancreatin r. + alkali.
Ury[15]	1904	Carcinoma pancreas	+	0	60	28	
Alexander and Ury[16]	1904	Chronic pancreatitis	+	0	Low.	Less than 50	Split fat in nine cases varying from 9 to 86 per cent.
		Chronic pancreatitis (7 cases).	+ 0	0	Low.	Low.	
Brugsch[18]	1906	Carcinoma pancreas with complete obstruction bile and pancreatic ducts.	0	+	61	15	Mixed diet.
					66	11	Milk and rice diet.
		Pancreatic abscess	0	0	79	40	No icterus.
			0	+	71	38	Slight icterus.
		Early pancreatic carcinoma	0	0	80	36	
		Obstruction pancreatic duct	0	0	75	30	
Adler and Milchner[17]	1908	Tumor of pancreas	+	0	....	64—85	Pancreon improved the splitting, but not absorption of fat.
Barbour	1911	Chronic pancreatitis following cholecystitis.	0	0	55.8	95.7	Without therapy.
					47.6	97.8	Hydrochloric acid.
					54.2	95.3	Pancreatin (not rhenania).

TABLE 2.—EXPERIMENTAL PANCREATITIS IN DOGS

Author	Date	Condition	Per Cent. N. Absorption	Per Cent. Fat Absorption	
Abelmann[18]	1890	Total extirpation of pancreas (18 cases).	Average 44	00	Non-emulsified fat fed.
				18.5	Emulsified fat fed.
				50–53	Milk fed.
			74–78	48–72	Pigs' pancreas fed.
			47–55		"Pancreatinum" fed.
		Partial extirpation of pancreas (12 cases).	Average 54	25–65	Emulsified fat fed.
				65–80	Milk fed.
Cavazzani[2]	1893	Total extirpation of pancreas.	Low.	Low.	Animal scorned fat, took soaps greedily.
Baldi[2]	1894	Total extirpation of pancreas.	.....	Low.	Large amounts of oily fat in stools.
Sandmeyer[19]	1895	Nearly total extirpation of pancreas (several cases).	62–70	0–78	Raw pancreas raised absorption; non-emulsified fat fed.
				42	Emulsified fat fed.
Rosenberg[20]	1896	Animal living 11 months with ligated pancreatic duct.	Low.	Low.	No change first month.
Oser and Katz[1]	1898	Ligation of pancreatic duct..	Normal.	Normal.	48 per cent. of fat split.
		Total extirpation of pancreas.	Low.	.....	Several cases.
			Normal.	Normal.	Severe diabetes forty-one days.
Zunz and Mayer[21]	1904	Ligation of pancreatic duct in 50 dogs.	.....	Low.	.....
Brugsch	1906	"Subtotal" pancreas extirpation.	.....	81	Milk diet.
				95	Olive oil diet.
		Total pancreas extirpation...	.....	50	Milk diet.
				9–20	Meat diet.
Camus and Nicloux[23]	1910	Ligation of biliary and pancreatic ducts.	.....	33–37	Without "lipaseidine."
			.....	63.8	With "lipaseidine."

nitrogen absorption figure, the greater importance in pancreatitis. It is more consistently low, and its significance is neither so much obscured by a complicating biliary obstruction nor as markedly affected by variations in diet as is the fat. A third factor which may complicate the fat metabolism, is the diabetic acidosis. Brugsch brings this forward to explain Sandmeyer's experimental work (Table 2), in which the latter obtained absorption figures for fat varying from 0 to 78 per cent.

Our metabolism work (Table 3 and Chart 1) is divided into three periods: Nov. 23-29 (no therapy); Nov. 30-Dec. 4 (hydrochloric acid dil. ℥xv with meals); Dec. 5-6 (pancreatin gr. vi, t. i. d.). The Schmidt-Strasburger[24] diet was given for the first four days. It contains in one day's portion: 1.5 liters milk, 100 gm. zwieback, 2 eggs, 50 gm. butter, 125 gm. beef, 190 gm. potatoes, 80 gm. oatmeal. This represents about 10.9 gm. nitrogen, 111 gm. fat and 191 gm. carbohydrate, and is given in five separate meals. A mixed diet was given on the two following days, no analyses being made, after which were given special diets No. 3 and No. 4. These were similar to the Schmidt-Strasburger diet and the amounts of nitrogen and fat contained in each are noted in Table 3.

The total urine and feces for each 24-hour period was collected daily at 7 a. m. The analyses of excreta received on any given day are tabulated under the date immediately preceding.

The nitrogen estimations were made by the Kjeldahl method, and the fat was obtained by the usual ether Soxhlet extraction. In general the laboratory procedures were the same as those employed by Brugsch.

The tables show that the nitrogen absorption during the first period averaged 55.8 per cent. of the amount ingested. Hydrochloric acid was given during the second period, at the suggestion of Professor Barker, in the hope of favoring pancreatic activity by the stimulation of secretin, the patient's condition being one of marked anacidity as stated above. The nitrogen absorption, however, fell to an average of 47.6 per cent. for these five days, thus confirming the statement of Ehrmann and Lederer[25] that achylia and anacidity are favorable rather than inimical to pancreatic function. During the "pancreatin" period, the nitrogen absorption corresponded very closely to that of the first period.

In none of the four fat analyses were abnormal figures obtained, and we have noted above that the striking butter-like stools of the first few days were soon replaced by stools of a liquid brown character. The only explanation of this lies in the fact that after admission to the hospital, the diet contained limited amounts of fat given in easily absorbable form.

The nitrogen balance remained normal throughout the experimental period indicating that, in spite of deficient absorption, the patient was not forced to draw on his rather meager supply of tissue protein during this time.

The administration of pancreatin rhenania with alkali followed a few days after the conclusion of the metabolism studies, and rapid improvement then ensued.

TABLE 3

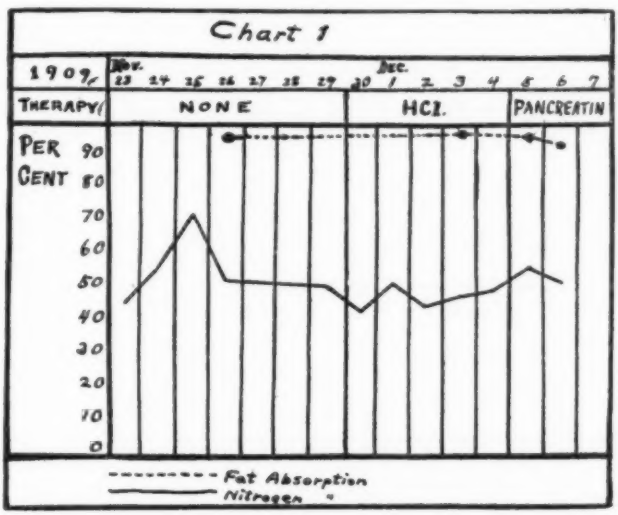
1909		November								December						
		23	24	25	26	27	28	29	30	1	2	3	4	5	6	7
Diet		Schmidt-Strasburger N = 10.9 Fat = 111.0				Mixed		No. 3 N = 5.98 Fat = 61.76					No. 4 N = 4.96 Fat = 70.05			
Therapy		None							Hydrochloric Acid					Pancreatin		
Urine	Total amount	620	1,050	790	1,450	1,190	740	935	410	1,040	920	860	600	550	300	440
	Nitrogen	6.3	6.4	6.9	5.2	.....	.....	2.76	2.60	1.98	2.87	2.00	2.96	3.00	2.01	...
Feces	Dry weight	13.06	29.36	12.64	12.10	24.22	13.88	4.12	6.99	4.88	.....	3.92	17.83	7.19	8.45	...
	Nitrogen	5.9	4.9	3.0	5.1	.....	.....	3.00	3.35	3.00	3.22	3.02	3.46	3.06	3.32	...
	Fat	.....	.....	.....	4.8	.....	.....	.....	.....	.....	.....	1.38	.....	2.53	4.12	...
Per cent. absorption	Nitrogen	45.9	56.0	72.5	53.3	.....	.....	51.1	44.0	51.1	45.2	47.9	50.0	56.1	52.3	...
	Fat	.....	.....	.....	95.7	.....	.....	.....	.....	.....	.....	97.8	.....	96.4	94.1	...
Nitrogen balance		—1.3	—0.4	+1.0	+6.0	.....	.....	—0.2	±0	+1.0	—0.1	—1.0	+0.4	+0.9	+1.6	...

The relation of the nitrogen and fat to the total dry weight of the feces was: nitrogen (average of thirteen analyses) 34.4 per cent.; fat (average of four analyses) 40.5 per cent.

OTHER FUNCTIONAL TESTS OF THE PANCREAS

Of the many tests devised for ascertaining the functional condition of the pancreas, but few have been proved of clinical value.

As indicative of impairment of the internal secretion, Loewi[26] supplements the tests for glycosuria or low sugar tolerance, with his epinephrin mydriatic reaction. It is based on certain very obscure and complex relations between the glands of internal secretion and the nervous system,



on which the metabolism studies of Eppinger[27] and others bear very interestingly. The practical value of the reaction is far from being established.

For the study of the function of the external secretion are available, on the one hand, the end products of metabolism, and on the other, the amounts and distribution of the enzymes themselves.

In addition to determining the presence of azotorrhea and steatorrhea and the quantitative study of these conditions with relation to the diet, we applied Schmidt's nuclei test. Centimeter cubes of beef were enclosed in silk and hardened in alcohol. After washing with water for three hours, several of these were given to the patient. They were later recovered in the stools and studied microscopically after treating with acetic acid. Very few nuclei were found intact. This negative result is

of little value as regards the action of the pancreatic juice, for nucleases, irrespective of trypsin, may occur in the intestinal tract. Had large numbers of nuclei been found, however, or had only the peripheral fibers of each cube given evidence of digestion, the result would have been very suggestive of pancreatic insufficiency.

The amount of lecithin in the feces was comparatively large in Deucher's three cases of pancreatitis, and later workers have not disproved that such an increase may be of value as a functional indicator.

Gerhardi,[28] in 1886, stated that, especially in intestinal obstruction, a low output of indican signifies decreased proteolysis, due to pancreatic insufficiency. Later observations on this point have been widely diverse, an increased output being shown in many cases. Controlled tests showed no indicanuria in the present case, but it must be borne in mind that peristalsis was rather rapid.

The pancreatic ferments themselves are made the basis of certain functional tests. For trypsin in the feces, we employed the casein test of Gross.[29] It is based on the fact that casein in an alkaline solution will disappear in the presence of trypsin. The addition of dilute acetic acid demonstrates the presence or absence of casein after time has been allowed for digestion. Trypsin was present in the feces during our metabolism work and in January, 1911.

Goldschmidt[30] offers a quantitative modification of the Gross test.

Schlecht,[31] following E. Müller, demonstrates proteolytic action by the formation of a hole in solidified serum, on which a drop of the ferment-containing fluid has been placed.

Sahli's[32] well-known glutoid capsules resist gastric action, but are soluble in pancreatic juice. An indicator, such as iodoform, is thus set free in the duodenum, and may be detected in the saliva or urine. This, again, has been found an unsatisfactory test for pancreatic impairment. Its chief value is in indicating the motility of the stomach.

The feces may be tested for lipase with the ethyl butyrate test of Kastle and Loevenhart.

The third pancreatic ferment, diastase, was neglected as an indicator until 1907, when Ambard, Binet and Stodel[33] suggested that tests be made for it after administration of a purgative. Purging in the normal individual produces a stool containing abundant diastase. This test has been extended by Wynhausen,[34] using the method of Wohlgemuth, for detection of the ferment.

We are not confined to the feces, however, for evidences of pancreatic juice in the alimentary canal. Boldyreff[35] has shown that an "oil breakfast" will cause a back flow of pancreatic juice and bile from the duodenum into the stomach. He gave 100 to 200 c.c. of 2 per cent. oleic acid in olive oil. One-half to an hour later he removed the stomach

contents, in which could be demonstrated the pancreatic ferments. Volhard states that olive oil alone may be used. According to Ehrmann and Lederer, the stomach contents, if acid, should first be neutralized.

Salomon suggested the feeding of "pancreon" and similar preparations as a therapeutic test of pancreatic insufficiency.

The much discussed reaction of Cammidge[36] has yet to be mentioned. This worker has claimed a specificity for certain crystals obtained after a complicated chemical procedure in the urine of pancreatitis. Much evidence has now accumulated to indicate that the test is not only cumbersome, but almost without significance. Last year Dr. G. H. Whipple[37] and others showed that similar crystals may be obtained from the products of autolysis of tissues and other sources. Negative tests were obtained in fifteen of nineteen cases of pancreatitis reported by Deaver[38] in his recent discussion of chronic pancreatitis from a surgical standpoint. Kinney has reported 154 various cases in which the test has been applied.

Cammidge himself has modified his procedure in several ways. For example, 10 c.c. of urine was at first asserted to suffice for the reaction; while his present method requires 4 liters — a very suggestive discrepancy.

Using the "C" reaction, 50 c.c. of urine from this patient gave a negative result. When 4 liters were taken, large yellow "sheaves" were isolated which dissolved in dilute sulphuric acid. Their melting point, however, was 130 F., instead of 170 to 180 F., as observed by Cammidge.

CONCLUSIONS

1. The case described is one of chronic insufficiency of the external secretion of the pancreas subsequent to acute cholecystitis.

2. There has been no diabetes at any time.

3. While azotorrhea and steatorrhea were both marked features on admission, the fat absorption was over 95 per cent. during the metabolism observations.

4. The nitrogen absorption during a period without therapy averaged 55.8 per cent. While hydrochloric acid was given, the average was 47.6 per cent. During the feeding of pancreatin (not rhenania) 54.2 per cent. of the ingested nitrogen was absorbed.

5. The nitrogen balance was normal during the metabolism work.

6. Rapid improvement followed the administration of pancreatin (rhenania) and calcium carbonate.

7. None of the other functional tests applied to the case gave significant results.

8. From 4 liters of urine atypical "Cammidge crystals" were isolated.

It affords me the greatest pleasure to express to Professor Barker my gratitude, not only for the opportunity of carrying on this work in the wards and the chemical laboratory of the medical clinic, but also for his kindly interest in the work and his many helpful suggestions.

I am further very much indebted to Dr. E. A. Slagle for most valuable assistance in the chemical work.

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THE METABOLISM IN A CASE OF IDIOPATHIC OSTEOPSATHYROSIS *

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To the kindness of Dr. B. Sachs, to whose service at Mt. Sinai Hospital this case was admitted on Oct. 16, 1909, is due the opportunity of making this study. A synopsis only of the history and clinical features is given, as the case will subsequently be presented from the clinical point of view by another hand.

Patient.—B. G., male (admission number 111186); family history and previous history yield nothing of importance. Venereal infection denied; no drug habits; no acute infection preceding onset.

Present Illness.—About fourteen months before admission patient broke right humerus in the upper third with very slight trauma. Two weeks after this injury he broke the left humerus in the upper third while raising the window. Both fractures healed very quickly. Following these injuries patient noticed that he was growing weak and thin; the muscles of both arms were beginning to atrophy and his strength rapidly diminished. Before the illness patient weighed 130 pounds. The atrophy of the arm muscles was followed by a rapid wasting of all the skeletal muscles. For twenty-four weeks previous to admission he has been unable to walk, and raises himself to a sitting posture with great difficulty; no pain or paresthesias. Five weeks before admission a bottle fell on his right arm and cracked the bone, as shown by *x*-ray. This fracture has since healed. Of late he has been complaining of headaches; no vertigo; no difficulty in swallowing; no urinary disturbance; bowels constipated; appetite fair; vision and hearing good.

First Physical Examination.—October 16, 1909. General condition poor; patient pale and emaciated.

Head: Fairly well formed; forehead receding. Expression dull; no skull tenderness; marked general alopecia. Speech normal.

Eyes: Right pupil somewhat larger than left and irregular; pupils react promptly to light and accommodation. No palsies of orbital muscles; no nystagmus. Conjunctivæ pale; corneal reflex present.

Face: No palsies; jaw reflex present; sensations normal.

Mouth: Teeth and gums in very poor condition; marked fetor. Throat negative. Pharyngeal reflex present.

Skin: Few scattered scars on back and extremities, not pigmented.

Glands: Palpable inguinals, axillaries, posterior cervical and small epitrochlears.

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*From the Laboratory of Physiological Chemistry, Mount Sinai Hospital, New York.

Thyroid: Showed no evidence of abnormality.

Chest: Marked atrophy of all muscles. Narrow; emphysematous; marked depressions above and below clavicles.

Lungs: Posteriorly, marked hyperresonance over bases, otherwise negative.

Heart: Showed no abnormality. Marked sclerosis of radial arteries. Tension normal.

Liver and Spleen: Negative.

Abdomen: Superficial reflexes present; cremasteric reflexes present. No abnormality.

Genitals: Negative.

Extremities: Upper; No ataxia; no tremor. In upper part of left humerus there was a callus at site of the old fracture. At junction of upper third and lower two-thirds of right humerus there was slight thickening of bone (old fracture).

Lower: Patient walked with great difficulty; gait uncertain, waddling, "goose-like." Power in both legs equally diminished in all groups of muscles. No ataxia or tremor. Knee-jerks increased on both sides; achilles reflexes increased. No clonus, Babinski, Mendel, nor Oppenheim. Sensation normal.

October 18 (Dr. Sachs): Atrophy (especially of arm and leg muscles), and stiffening. Considerable stiffening of upper part of spinal column. Forearm muscles little affected, deltoids hardly. Interosseous spaces in both hands very distinct. Hand muscles wasted, especially hypothenar of left hand. Reflexes of upper extremities lively. On striking forearm at any point there is contraction of biceps and pectoral group of same side. Grasp of both hands good. Difficulty in getting up from chair. Patient rises from chair as one suffering from muscular dystrophy and shows weakness of the deep spinal muscles below the mid-dorsal level. When placed on the floor and asked to rise, he is unable to do so, chiefly on account of the weakness of the spinal muscles. Marked atrophy both anteriorly and posteriorly of leg and arm muscles. There is no bulbar paralysis present. All muscular groups of extremities respond to strong faradism only. In some groups the response is feeble. No fibrillary twitchings.

Course of Disease.—October 30: Sputum negative for tubercle bacilli.

November 2: Condition much better; gained nine pounds since admission and is much stronger. Able to rise from floor, but still with great difficulty. Local muscular irritability less marked. Otherwise no change.

November 3: No disturbance of pain or temperature sense.

Discharged Nov. 15, 1909.

Readmitted Dec. 13, 1909.

Jan. 1, 1910: Complains of some pain in legs; has gained considerably in weight. Able to rise from floor with assistance. Gait still waddling. Weakness of ilio-psoas muscles chiefly; gluteal wasting. Wasting of arm muscles, less of intrinsic hand muscles. Reflexes unchanged.

January 10: On discharge, condition about same as on admission; slight gain in weight.

Readmitted Dec. 20, 1910, complaining of marked weakness.

Second Physical Examination.—General condition fair; marked emaciation. Pupils equal, reacting. Upper extremities: Limitation of motion of right shoulder joint and slight of left shoulder. Marked atrophy of muscles of both forearms. Lower extremities: Loss of power in right leg; power slight in left. Marked atrophy in muscles of thigh. In middle of right tibia, on anterior sur-

face, was a small swelling about three-fourths of an inch in diameter, fluctuating, not tender, slightly movable. Otherwise unchanged since last stay in hospital. Vomited frequently on and after December 23.

Died Dec. 29, 1910. An autopsy was not permitted.

Temperature during patient's earlier stays in hospital always below 99. A few days before death reached 99.4 F., and pulse which had previously been normal in frequency, ranged between 90 and 110. Respirations, except during terminal period, normal in frequency.

Wassermann and Noguchi reactions, Nov. 12, 1909: Negative (Dr. D. J. Kaliski).

Blood Examination.—Oct. 19, 1909: W. B. C. 11,000; R. B. C. 4,300,000; hemoglobin 85 per cent. Differential count: Polynuclears 76 per cent.; large lymphocytes 14 per cent.; small lymphocytes 10 per cent.

November 2: Blood-pressure: Right arm, 143 mm. mercury. Left arm, 138 mm. mercury.

Weights:

Oct.	17, 1909:	86 pounds.
Oct.	22, 1909:	89 pounds.
Oct.	24, 1909:	92½ pounds.
Oct.	31, 1909:	95 pounds.
Nov.	7, 1909:	94 pounds.
Nov.	14, 1909:	96 pounds.
Dec.	17, 1909:	95 pounds.
Dec.	24, 1909:	94½ pounds.
Dec.	26, 1909:	95 pounds.
Jan.	3, 1910:	98 pounds.
Jan.	10, 1910:	97 pounds.

Weight not recorded during last stay in hospital.

Average daily amount of urine passed during stay in hospital: 2200 c.c. Specific gravity of single specimens varied from 1004 to 1034; faint traces of albumin; no sugar, acetone, nor diacetic acid was found at any time. Hyaline and granular casts in small number were repeatedly found.

Röntgen Ray Examination (Dr. L. Jaches).—Oct. 24, 1909: One radiographic plate of the left shoulder shows the head, anatomical and surgical necks of the humerus to be cystic; the shaft shows a sponge-like appearance.

Oct. 27: Two radiographic plates of hips and right shoulder-joint show cystic condition of bones with partial and irregular absorption.

If this case be considered one of osteopsathyrosis, it is in some respects unique, viz.

1. It showed marked and general muscular atrophy and weakness.
2. It was accompanied by polyuria.
3. It came at a more advanced age than most of the cases on record.
4. There is no hereditary element in the etiology.

As far as could be ascertained, there is in the literature of this disease only one case[1] in which special mention is made of the presence of

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muscular atrophy. Here it is mentioned that with otherwise well-developed musculature, there was marked atrophy of the muscles of the calves. The presumption is that it was due to disuse. Poirrier[2] regards the muscular atrophy as the result of multiple fractures. This atrophy, he states, most often relates only to the muscular groups in relation to the fractured bone. Larat, Roger and Voisin,[3] in a recent study of the muscular reactions in their case found marked diminution of the electrical reaction of the muscles, this being general and not confined to the site of fracture. They consider the muscular lesions as contemporaneous with the osseous changes, as they appear to have been in the present case.

As to the chemical composition of the bones in osteopsathyrosis, we have only the statement of Enderlen, who reports that in his case there was an increase of organic substance and a decrease of mineral matter. The diagnosis in this case, however, appears to be open to doubt.[4]

No case of osteopsathyrosis has been investigated with reference to the metabolism. The only statement bearing on it is that of Blanchard, who found an increase of P_2O_5 in the urine. This finding taken by itself is of no value.

RESULTS OF METABOLISM DETERMINATION

I. DAILY URINARY RESULTS

Date	Total N	Creatinin	Creatinin N	Creatinin N in % of Total Urinary N	Amount in c.c.
12/19/09	11.656	0.9525	0.353	3.02	2350
12/20/09	13.294	0.764	0.283	2.12	2380
12/21/09	9.243	0.634	0.235	2.55	1680
12/22/09	13.995	0.942	0.349	2.49	2840
12/23/09	10.643	0.709	0.263	2.47	2210
12/24/09	8.561	0.554	0.205	2.39	2080
Totals	67.392	4.528	1.688		

Creatinin coefficient = mgm. creatinin nitrogen excreted daily per kilo body weight $= \frac{0.281}{43} = 0.0065$.

Average of daily creatinin nitrogen in percentage of total urinary nitrogen = 2.5.

2. Poirrier, H. A.: L'osteopsathyrose, Thèse de Paris, 1906-07, p. 103.

3. Larat, Roger and Voisin: Compt. rend. Soc. de biol., 1909, lxvi, 728.

4. Schmidt, M. B.: Ergeb. d. allg. Path., etc., 1897, iv, 576.

II. SUMMARY OF RESULTS FOR SIX-DAY PERIOD

Element	Urine	Feces	Total Excreted	Total in Food	Balance
CaO	6.2826	7.2853	13.5679	8.6279	— 4.94
MgO	0.5711	0.7576	1.3287	1.1458	— 0.1829
Total P	2.5666	0.8601	3.4267	3.986	+ 0.5593
Total S	6.3838	0.7822	7.166	8.0642	+ 0.8982
Total N	67.392	10.904	78.296	89.085	+10.789

III. ANALYTICAL METHODS

The metabolism was studied for a period of six days, the patient being allowed to eat freely of the ordinary hospital diet. Each portion was weighed or measured and an equal amount was sent to the laboratory for analysis. All the food was collected for the period, dried on the water-bath, reduced to a fine powder and sampled for analysis.[5] Only distilled water was consumed. Salt, butter and bread were weighed off in a quantity sufficient for the six days. The amount used was computed and these substances, except the butter, were added in appropriate amounts to the samples of food taken for analysis. Butter: For calcium, magnesium and total phosphorus 30 gm. were digested in Kjeldahl flask with H_2SO_4, made up to 1000 c.c. and of this solution 100 c.c. taken for each analysis. Total sulphur was not determined in butter on account of the difficulty encountered in making fusions. Neuberg[6] states that there are only traces present.

The stools were marked off with charcoal at the beginning and the end of the period.

Urine was collected for each twenty-four-hour period, and separate determinations of nitrogen, creatin and creatinin were made.

Total sulphur, total phosphorus, calcium, and magnesium were determined on a mixed specimen consisting of aliquot parts of each day's urine.

All determinations were made in duplicate, and analyses were repeated when the results for the pairs did not agree.

Total nitrogen—Kjeldahl.

Creatin and creatinin—Folin.

Magnesium and calcium—According to the method of McCrudden[7] except that the calcium was weighed as $CaSO_4$.

Total phosphorus and total sulphur—Fusion with solid sodium hydrate and potassium nitrate. Fusion mass dissolved in hot water, made strongly acid with HNO_3 and precipitated as ammonium phosphomolybdate, which was dissolved in ammonia, precipitated as $Mg\,NH_4PO_4$ and weighed as $Mg_2P_2O_7$. Total sulphur weighed as $BaSO_4$.

The diet for six days was as follows:

Dec. 18: Milk, 32 oz.; Meat, 147 gm.; Vegetable, 210 gm.; Soup, 14 oz.; Crackers, 17 gm.; Zwieback, 10 gm.; Oatmeal, 120 gm.; Egg, 47 gm.; Water, 24 oz.

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5. McCrudden, F. H.: Jour. Med. Research, 1903, iv, 135.

6. Albu and Neuberg: Physiologie und Pathologie des Mineralstoffwechsels, Berlin, 1906.

7. McCrudden, F. H.: Jour. Biol. Chem., 1910, vii, 83.

Dec. 19: Oatmeal, 120 gm.; Milk, 24 oz.; Egg, 180 gm.; Cracker, 17 gm.; Water, 40 oz.; Zwieback, 17 gm.; Meat, 195 gm.; Cocoa, 8 oz.; Potatoes, 120 gm.; Custard, 30 gm.; Ice Cream, 65 gm.; Apple Sauce, 140 gm.; Prunes, 55 gm.

Dec. 20: Meat, 92 gm.; Oatmeal, 117 gm.; Cabbage, 112 gm.; Milk, 16 oz.; Custard, 40 gm.; Water, 40 oz.; Soup, 8 oz.; Cocoa, 8 oz.; Cream, 1 oz.; Potatoes, 110 gm.; Orange Juice, 3½ oz.; Rice, 145 gm.; Farina, 183 gm.; Egg, 93 gm.

Dec. 21: Oatmeal, 45 gm.; Water, 48 oz.; Milk, 40 oz.; Cocoa, 8 oz.; Meat, 75 gm.; Rice, 135 gm.; Potatoes, 114 gm.; Custard, 75 gm.; Prunes, 60 gm.; Soup, 8 oz.; Cream, 1 oz.; Apple Sauce, 175 gm.; Egg, 94 gm.

Dec. 22: Oatmeal, 220 gm.; Egg, 160 gm.; Milk, 40 oz.; Water, 40 oz.; Chicken, 60 gm.; Rice, 180 gm.; Potatoes, 150 gm.; Soup, 8 oz.; Custard, 35 gm.; Cream, 1 oz.; Farina, 205 gm.

Dec. 23: Oatmeal, 200 gm.; Egg, 45 gm.; Milk, 16 oz.; Water, 32 oz.; Cocoa, 8 oz.; Potatoes, 100 gm.; Soup, 8 oz.; Chicken, 70 gm.; Rice, 160 gm.; Cabbage, 100 gm.

From Dec. 18 to 23: Bread, 639.2 gm.; Butter, 92 gm.; Salt, 13 gm.

Except in one particular — the small retention of magnesium — my results are strikingly similar to those of McCrudden[8] and the less complete findings of earlier workers on the metabolism in osteomalacia. It will be noted that hand in hand with a retention of nitrogen went a relatively enormous loss in calcium and a retention of sulphur and of phosphorus. The loss of calcium occurred in spite of a large excess of this element in the food over the normal needs of the human body. Towle[9] found that CaO, 0.014 gm. per kilo body weight, were needed daily. Renvall[10] found that an adult man needed Ca 0.7 (CaO 0.98) per day. The patient under consideration received daily CaO 1.322 = 0.03 per kilo.

In this case the muscular atrophy and weakness were prominent factors, and it is of interest to note that in part the findings are paralleled by those in cases where muscular atrophy was not complicated by such obvious bone lesions.

Thus, Johannes Mueller[11] states that in a case of progressive muscular atrophy, there was found an increased excretion of sulphur and calcium. This, however, he ascribes to a secondary atrophy of the bones. Pemberton, in a case of myasthenia gravis, found a marked loss of calcium amounting to 8.888 gm. in the ten days of the investigation. In another paper[12] he states that no study of calcium metabolism is on record, in either muscular dystrophy or Thomsen's disease. In his case

8. McCrudden, F. H.: Am. Jour. Physiol., 1905, xiv, 211; 1906, xvii, 211.

9. Towle: Am. Jour. Med. Sc., 1910, cxl, 100.

10. Renvall, G.: Skand. Arch. f. Physiol., 1904, xvi, 94.

11. Mueller, Johannes: Habilitationsschr., Wurzburg (Abstr. in Arch. f. Verdauungskrankh., 1897-98, iii, 282.

12. Pemberton: Am. Jour. Med. Sc., 1911, cxli, 253.

of myotonia atrophica, studied for five days, with a positive nitrogen balance of 28.265 gm. there was a negative calcium balance of 0.566 gm.

In both of the above muscular diseases he found a decrease of creatinin in the urine as compared with the normal. Spriggs[13] found a similar relationship in progressive muscular dystrophy, myasthenia gravis and amyotonia congenita.

The creatinin findings in the case under consideration were not obtained on a meat-free diet. On this account the creatin values are not given. The amount of preformed creatinin is, however, so little affected by a moderate amount of meat in the diet[14] that we can disregard this factor. The creatinin ratio in this case was only slightly below the normal, which is from 7 to 11 mg., although the percentage of creatinin-N to total urinary N is considerably below that found in normal cases (3.9). Whether this relationship alone would justify a conclusion that the muscular changes present played a minor rôle in the causation of changes in the mineral metabolism can be determined only by further calcium and creatinin determinations in suitable cases.

Mention has already been made of the similarity of the findings in this case to those in osteomalacia. The latter disease has been checked by castration, and McCrudden, in his case, found the consequent improvement in the symptoms to be accompanied by calcium retention, where before there had been a loss. Similar results were obtained by Neumann. Of late this disease has been shown to be amenable in some cases to injection of epinephrin.[15] Bossi[16] also believes that this substance has a similar influence in the pelvic deformities of rickets.

Carnot and Slavu[17] have shown that in dogs injected subcutaneously with epinephrin (*chlorhydrate d'adrénaline*) ossification is much greater than in controls. They state that it seems to cause calcium retention.

These facts and many others point to a close relationship between changes in the bones and in calcium metabolism, and the functions of the organs of internal secretion. Thus, Tansk and Vas[18] found a slight loss of calcium in acromegaly. Oberndörrfer[19] found a much more marked

13. Spriggs: Quart. Jour. Med., 1907, i, 68.

14. Van Hoogenhuyse and Verploegh: Ztschr. f. physiol. Chem., 1908, lvii, 161. Folin, O.: Festschr. f. Hammarsten, Upsala, 1906; Klercker, Otto af: Beitr. z. chem. Physiol. u. Pathol., 1906, viii, 60. Shaffer, P. A.: Am. Jour. Physiol., 1908, xxii, 449.

15. Bossi: Centralbl. f. Gynäk., 1907, Nos. 3 and 6. Stocker: Corr.-Bl. f. Schweiz. Aerzte, 1909, xxxix, 433.

16. Centralbl. f. Gynäk., 1907, xxxi, 1560.

17. Carnot and Slavu: Soc. biol., 1910, lxviii, 832.

18. Tansk and Vas: Pest. med.-chir. Presse, 1899, xxxv, 194.

19. Oberndörrfer, E.: Ztschr. f. klin. Med., 1908, lxv, 6.

loss amounting to CaO 8.77 gm. in a ten day period. In cretinism ossification is delayed.[20]

Various observers have recently shown in experiments in animals that thymectomy leads to marked changes in the bones, rendering them softer and more flexible,[21] or leading to spontaneous fracture.[22] These changes are especially marked in very young animals in which the bone is found to be largely replaced by cartilage.[23] Klose and Vogt[24] have found that this operation causes a reduction of more than one-half in the calcium content of the bones, and Fraenkel[25] states that the thymectomized animals excrete more than twice as much calcium as the controls.

Parathyroidectomy, McCallum[26] found, caused in dogs an increase in calcium in the urine. Other observers have had varying results.

For the hypophysis Franchini[27] has found that injection of its extract causes a marked calcium and magnesium deficit, and a smaller loss in phosphorus. The influence of the isolated posterior lobe on metabolism was especially profound. Falta[28] also states that the hypophysis has a very marked influence on calcium and magnesium metabolism. Malcolm[29] found that feeding the dried glandular portion caused increased calcium excretion with a considerable increase also in magnesium, and that the dried nervous portion also increases calcium excretion, but that magnesium is less affected. With the fresh gland, however, calcium retention ensued.

These facts have been mentioned because the coincidence of rapid wasting, spontaneous fractures, and a marked polyuria (which does not seem to be adequately explained by the slight evidences of nephritis) seems to point to some disturbance of the organs of internal secretion. That the hypophysis may have played an important part here is suggested by Cushing's summary[30] of the results of injection and feeding experiments with this gland. He states that "in the posterior lobe or its epithelial investment is a substance which raises blood-pressure, dilates the pupil, causes diuresis, and, when given subcutaneously or injected over long periods of time, is likely to produce marked nutritional disturbances."

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20. Schmidt, M. B.: Ergebn. d. allg. Path., 1897, iv, 617.
21. Basch: Jahrb. f. Kinderh., 1906, lxiv, 285.
22. Klose: Arch. f. Kinderh., 1911, lv, 1.
23. Soli: Arch. ital. de biol., 1909, lii, 217.
24. Klose and Vogt: Beitr. z. klin. Chir., 1910, lxix, 1.
25. Fraenkel, S.: Dynam. Biochemie, Wiesbaden, 1911, 447.
26. McCallum and Voegtlin: Bull. Johns Hopkins Hosp., 1908, xix, 91.
27. Franchini: Berl. klin. Wchnschr., 1910, xlvii, 613.
28. Falta: Wien. klin. Wchnschr., 1909, lix, 1059. Falta and Ivcovic, ibid, p. 1806.
29. Malcolm, J.: Jour. Physiol., 1903, xxx, 270.
30. Cushing, H.: Amer. Jour. Med. Sc., 1910, cxxxix, 475.

While the facts in this case point toward a disturbance of the organs of internal secretion, it is not intended to select one or another of them as the one primarily at fault. Both experimental and clinical investigations show that a disturbance of one of these glands is quickly followed by changes in others of the system.

McCrudden[31] has already suggested an etiological similarity between rickets, osteitis deformans, and senile and puerperal osteomalacia, and to this we may add osteopsathyrosis. If the common factor in these conditions should prove to be some disturbance of the organs of internal secretion, this case would add evidence that they also play an important part in the pathology of the muscular atrophies.

I wish to express my thanks to Dr. I. Abrahamson for many kindnesses in connection with the work, and to Dr. S. Bookman for suggestions in regard to the analyses.

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31. McCrudden: The Archives Int. Med., June 15, 1910, v, 630.

THE COAGULATION-TIME OF THE BLOOD AS AFFECTED BY VARIOUS CONDITIONS

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An estimation of the coagulation-time of the blood is of little value unless one is acquainted with the many factors that affect it. Some of these factors are extrinsic, acting on the shed blood; others are intrinsic, acting on the blood while it is still in the vessels. Of the former factors many are introduced by the method employed for measuring the clotting-time. The clotting-time obtained by any one of the different methods employed is influenced by the factors of error inherent to that method. It is important, therefore, to be familiar with the sources of error inherent in the method used.

1. METHODS EMPLOYED FOR MEASURING THE CLOTTING-TIME OF THE BLOOD

The methods employed for measuring the coagulation-time of the blood may be grouped according to the similarity of the factors involved. In one group the blood is received in capillary tubes, in another on wire loops; the contour of the drop is observed in several methods, the movement of the corpuscles when a current of air is directed against the drop in others, and the first appearance of shreds of fibrin in the drop in still others. Some methods require the chemical treatment of the drop.

1. METHODS IN WHICH THE BLOOD IS DRAWN INTO CAPILLARY TUBES

1. Vierordt's Method.—Vierordt allowed the blood to flow into capillary tubes, 1 mm. in diameter and 5 cm. long, until a column 5 mm. long was obtained. A white horsehair, about 10 cm. long, was introduced into each tube and drawn out slowly from time to time. It is not colored so long as the blood remains fluid. Coagulation begins when shreds of fibrin cling to the hair, and is completed when no more coagula are deposited on it.

2. Koffman and Lidsky's Modification of Vierordt's Method.—Koffman and Lidsky made possible tests at a constant desired temperature. A corked glass tube is passed through the cork into a horizontally placed thermoflask, filled with water of the desired temperature, usually 15 C. Extending into the glass tube through its cork, are a thermometer and a metal rod, to which are clamped in line small capillary tubes through which a horse-hair passes.

3. Wright's Method.—Wright uses capillary tubes of equal length and caliber, the latter being about 0.25 mm. The finger is pricked and at quarter-minute or half-minute intervals a column of blood about 5 cm. in length is aspirated into the tubes one at a time and drawn a little way up from the orifice. Two minutes after it is filled, the investigator blows down the first tube. If the blood cannot be dislodged, it is called "clotted"; otherwise it is designated "liquid" or "clotting," as the case may be. The other tubes are then examined similarly, the time from the appearance of the drop on the finger until it blocks the tube being regarded as the clotting-time. To keep the tubes at a constant temperature of 37 C. or 18.5 C., they are, both before and after being filled with blood, placed with a thermometer in the pockets of a flannel bandage, which is fitted tightly about a tin can containing water kept at the necessary temperature, or they are immersed in a tumbler, or can, of water maintained at the desired temperature. In the latter instance rubber caps are fitted over the ends of the tubes before they are filled with blood. Either the finger is punctured but once, a ligature which has been placed about it being relaxed at frequent intervals, or a fresh prick is made for each tube.

4. Fox's Modification of Wright's Method.—Hingston Fox obtains the blood as does Wright, but applies a rubber nipple to the tube and expresses the blood into water, regarding coagulation to have occurred when the blood no longer diffuses in the water but remains as a definite worm-like clot, or when the blood is expressed with difficulty. He keeps the tubes at room temperature and reduces his observations to a standard temperature of 60 F.

5. McGowan's Method.—McGowan binds a rag tightly around a finger, ten seconds later pricks it, and, applying a capillary tube 6 inches long with a uniform bore of 1.5 mm., in ten seconds fills it for 4 inches in a continuous flow. The column of blood is then allowed to run down the tube and the end through which the blood entered is fused in a flame or is sealed with wax or paraffin. Care being taken not to hold the tube between the blood and the sealed end, the tube is laid down with a thermometer alongside, and at the end of each minute a file mark is made on the tube half an inch or less from the end of the column of blood that is remote from the sealed end of the tube. This piece of tube is then broken off, care being taken in breaking it to keep the two ends of glass approximated. The two ends of glass are then drawn apart, and the first stage of coagulation visible to the naked eye is shown by a minute shred of fibrin stretching between the two broken ends. When this is reached, the other parts of the tube are similarly broken to confirm the first observation.

6. Addis's Modification of McGowan's Method.—Addis places McGowan's tubes in a glass cylinder which is placed in a metal cylinder covered with asbestos, the lid of which has three openings: one for the part containing the capillary tubes, one for a brass tube containing a thermometer, and one for a tube through which hot water is introduced so that both cylinders shall be filled with water maintained at a constant temperature of 20 C. He does not regard as indicating the end point of coagulation the fine filament of fibrin seen when the end of the tube is broken off, but regards rather the appearance of a thread of fibrin only in the last inch of blood. Addis takes the average of three tubes.

7. Rudolf's Modification of McGowan's Method.—To heat the tubes at a constant temperature Rudolf employs a pint vacuum bottle, replacing its ordinary cork with a rubber one perforated in three places to accommodate a thermometer and two brass tubes, 7 inches long and just large enough in caliber to hold easily the glass blood tubes.

8. Mercier's Modification of McGowan's Method.—The bore of the capillary tube is immaterial in Mercier's method, which otherwise is the same as McGowan's up to the point of filling the tube. Then, instead of sealing the end of the tube, Mercier blows the drop at once onto a glass surface. Sealing the end of the tube he uses the sealed end as a rod to dip from time to time in the drop of blood, noting as coagulation the very definite moment at which the rod draws from the drop a fine thread of fibrin.

9. Sabrazès' Method.—Sabrazès in 1899 devised a method which he perfected five and seven years afterward. His tubes, in which coagulation is determined in the same manner as in McGowan's method, are 5 cm. long with an internal diameter of 1 mm. Three such tubes are filled with the second, third and fourth drops, respectively, that exude on a prick, so that the column of blood occupies about the middle of the tube. Sabrazès makes a file mark previous to the commencement of the experiment and as soon as he fills the tubes, places them in close proximity to the fine bulb of a special thermometer in the upper compartment of a glass box divided into two parts by a glass partition, the lower compartment containing hot water in winter and ice in summer, so as to keep the temperature at 18.5 C.

10. Schultz's Method.—Schultz modifies the capillary tube by having one 4 inches long blown out into twelve or more regular expansions—tiny bulbs, or hollow beads—with short spaces between. The tube is filled with blood and at definite intervals the beads are broken off, one at a time, and shaken in a measured quantity of physiological salt solution. He designates as the end stage that point at which the bead remains filled with the clot and on shaking it only a very small quantity of red blood cells drops into the solution to color it.

II. METHODS IN WHICH THE CORPUSCLES ARE SET IN MOTION BY MEANS OF A CURRENT DIRECTED AGAINST A DROP OF BLOOD

1. Brodie-Russell Method.—The Brodie-Russell instrument consists of a small, deep, circular air-chamber, closed below by a glass plate, on which lies a layer of water, and roofed in above by a metal ring, in which is fitted an inverted truncated glass cone. The air-chamber is surrounded by a water-jacket, which has inflow and outflow tubes, so that the temperature of the air-chamber can be regulated. The water-jacket is pierced by a metal tube, to the interior of which is fitted a glass tube, drawn out to a fine orifice which is directed toward the lower surface of the cone. A rubber bulb is attached to the outer end of this tube.

The glass cone is removed and its lower surface is dipped carefully into a drop of blood so that the whole of the surface is exactly wetted by the blood. The cone is then placed in position in the air-chamber, and by gently compressing the bulb a fine stream of air is thrown on the edge of the drop of blood, setting the corpuscles in motion. Coagulation has occurred when the movement ceases, as observed under the low power of the microscope.

2. Pratt-Grützner Modification.—Pratt and Grützner omit the water-jacket and the truncated glass cone. They cement a metal ring, about 0.875 mm. in height and 1.5 cm. in diameter, to an ordinary glass slide. Through a hole in this ring is fastened a small metal tube (or hypodermic needle), to the outer end of which is attached a rubber bulb. A drop of blood is picked up on a heavy cover-slip, which is placed, with the blood downward, on the ring, the upper rim of which having been previously coated with petrolatum.

3. Boggs' Modification.—Boggs also omitted the water-jacket but improved the glass cone. In his instrument the metal collar is pierced by a small hole, which allows an equalization of pressure in the chamber when the air is blown in. A few other slight alterations add to convenience in handling.

4. Addis' Modification.—Addis substitutes for intermittent jets of air at unknown and variable temperature, a continuous stream of oil at a known and constant temperature. He uses Boggs's air chamber, which he keeps full of mineral oil. A stream of filtered oil from a reservoir is directed by the fine nozzle of the small tube tangentially against the edge of the drop. The oil in its passage from the reservoir passes in a flexible metal tube through a water-bath kept at a constant temperature by means of Schäfer's gas thermometer, or, where gas is not available, by Gibson's electrical thermostat. Immediately after it has passed through the nozzle into the chamber and against the drop of blood, it impinges on the bulb of a fine thermometer, and the temperature of the oil immediately surrounding the blood can be read off.

III. METHODS IN WHICH THE BLOOD IS PICKED UP IN A WIRE LOOP

1. Biffi's Method.—Biffi's apparatus consists of a glass jar with a perforated cork containing a thermometer, with the reading above the cork, and a glass rod or tube into which is fused a platinum wire bent in such fashion as to have five loops of 3 to 4 mm. diameter 1 cm. apart. These loops are touched to the surface of a drop of blood so that each takes up a film of blood. The loops are then placed in the glass jar which is filled to a certain point with water at 20 to 25 C., the rod passing through the cork. At stated intervals the rod is pulled down so that one loop after another is introduced into the water. When coagulation is complete, the blood no longer diffuses into the water, leaving the loop perfectly clean, but remains unaffected as a solid red mass.

2. Goldhorn's Modification of Biffi's Method.—Goldhorn made the loops more permanent by giving the wire an extra twist so as to have the loop unalterably fixed on a little stalk. He also made them larger.

3. Buckmaster's Method.—Buckmaster makes an elliptical ring, about 6 to 9 mm. in the long diameter and 4 inches in the short, of fine platinum, silver or iron. This loop is swept through a drop of blood without touching the skin. The loop is given a shake to detach some blood, leaving a thin film of even thickness. The loop is then placed in a small moist chamber, kept at a temperature of between 30 and 40 C., the shank of the loop being clamped in a holder so that it can be rotated. Commencing in a horizontal position, it is rotated at intervals into a vertical position and examined with a magnification of about ten diameters. When the corpuscles in the film no longer fall under the influence of gravity, leaving a clear space above, but the blood remains of the same opacity throughout, coagulation has occurred.

IV. METHODS IN WHICH THE BLOOD IS OBSERVED FOR THE APPEARANCE OF FIBRIN

1. Simple Method with Slide and Needle, or Straw.—One of the simplest procedures for testing the clotting-time, which is still extensively employed, is mentioned by Murphy and Gould. A drop of blood is placed on a clean glass slide and its consistency is periodically tested by moving the drop with a needle. When the blood becomes gelatinous and fibrin shreds are thus demonstrable, coagulation has taken place. A similar method is described by da Costa. Several individual drops of blood of the same size are collected on the surface of a slightly warmed glass slide. At regular intervals of about one minute, a straw of a whisk-broom is lightly trailed through each drop in succession until sooner or later a delicate thread of fibrin may be observed clinging to the straw.

2. Schwab's Method.—Schwab observed the appearance of fibrin threads in a hanging drop. He takes a small drop of blood on a cover-

glass and quickly places it face downward on a slide with a concavity. The appearance of fibrin threads in the clear serum at the periphery of the drop, as viewed under the oil immersion lens, indicates the occurrence of coagulation.

3. Bürker's Method.—Bürker allows a drop of blood to fall into a drop of distilled water on a glass slide let into the lid of a box within which water is kept at a constant mean temperature of 18 C. Fine rods of glass are passed through the mixture of blood and water every half minute until a thread or a mass of fibrin is picked up.

4. Riebes' Modification of Bürker's Method.—Riebes uses a large glass slide with six concavities, which he fills with pure olive oil. One drop of blood is allowed to fall in each concavity and every half minute a fine wire, usually one used for cleaning hypodermic needles, is passed through one of the drops from below upward to the middle, so carefully that the drop is not subdivided. Throughout the test the slide is kept at a temperature of 20 C. Coagulation has occurred when a slight coagulum is raised over the level of the oil.

V. METHOD EMPLOYING ACTIVATED SERUM

Morawitz's Method.—The method described by Morawitz and by Birnbaum and Osten is based on the theory that blood-serum, made very active by the addition of caustic soda, can cause clotting in a fibrinogen solution. About 10 to 15 c.c. of blood are taken from a vein and kept cool in a beaker until the pressed-out serum settles. The latter is removed, centrifugated, and eventually filtered. To equal parts of this serum (5 c.c.) the same amount of a decinormal solution of sodium hydrate is added and after a quarter of an hour's action the lye is neutralized with decinormal sodium chlorid. Two c.c. of a clear and opalescent solution of fibrinogen, obtained from horse's blood, are placed in a test-tube, and with a pipette several drops—5 to 30—of the activated serum are added. The solution, at first fluid, gradually takes on an oily nature, and finally becomes gelatinized. The end point of clotting is the moment when the fluid surface begins to be uneven in the tilted test-tube.

VI. METHOD EMPLOYING ANTICOAGULANT SUBSTANCE

Chantemesse's Method.—Chantemesse mixes a minute volume of blood with the same volume of a solution of some salt preventing coagulation. To suppress coagulation of normal blood *in vitro* it is mixed with an aqueous 1 to 800 solution of potassium oxalate. When the coagulating force is greater, a stronger solution of oxalate is needed to oppose the formation of a clot; when the force is weaker, a weaker solution suffices. Several samples of blood are mixed with oxalate solutions of different strengths, 1-400, 1-600, 1-800, 1-1000, 1-1200, 1-1500, 1-1800, the mix-

ture being received and preserved in fine pipettes, like Wright's, and at the end of an hour a glance at the pipettes shows whether the coagulability is equal to, or greater, or less than normal.

VII. METHOD WHICH MEASURES THE MECHANICAL RESISTANCE OF COAGULATING BLOOD

Koffman's Coagulo-Viscosimeter.—Koffman devised an intricate apparatus in which the blood is received in a nickel vessel with an internal diameter of 1 cm. which is rotated in a water-bath by means of a clock-motor so that it makes twelve to fifteen turns per minute; projecting down into the middle of the vessel is a small silver blade fastened to a shaft, the upper end of which is connected with a pointer on a dial with 100 divisions. One end of a fine mainspring is attached to this shaft, the other end being fixed. This prevents the free rotation of the blade with the blood in the vessel and permits only a certain amount of turning. The amount of turning for the time being is proportional to the degree of coagulation of the blood examined and is easily read on the dial. A curve is made, the height representing the degree of turning and the base the number of minutes from the moment of puncture.

VIII. METHODS DEPENDING ON CHANGES IN THE CONTOUR OF THE BLOOD

1. Hayem's Method.—In Hayem's method, as described more fully by Bezançon and Labbé, a flat-bottomed glass test-tube, about 5 cm. high, with an interior diameter of 7 mm., is filled to a height of 3 to 4 cm. with blood as it flows from the wound. The tube is tilted at intervals, coagulation being completed when the blood becomes so solid that the level no longer changes with each movement of the tube.

2. Milian's Method.—In Milian's method a rather large drop of blood is allowed to fall on a glass slide, which at intervals is carefully tipped vertically. Coagulation has occurred when the drop, instead of becoming tear-shaped on tilting the slide, does not change its shape, but remains convex in outline.

3. Bezançon and Labbé's Modification of Milian's Method.—Bezançon and Labbé let three drops of blood fall on three slides which they place under a bell-jar and examine from time to time by tilting.

4. Hinman and Sladen's Modification of Milian's Method.—Hinman and Sladen pick up a series of drops by touching a slide to the drops and, placing the slide on a millimeter rule, wipe off all drops whose diameters are less than 4 mm. or greater than 5 mm. On tilting the slide, they observe not only the contour of the drop but also the changes in density when held to transmitted light, the dense portion being in the center when coagulation has occurred and at the lower edge when the drop is still fluid.

5. Schwarz and Ottenberg's Modification of Milian's Method.—Schwarz and Ottenberg take a drop of blood, 5 mm. in diameter, from a prick in the finger, on a cover-slip, which they invert on a hollow ground slide and ring with liquid petrolatum to prevent evaporation and exclude air currents. They determine the moment of coagulation by the failure of the drop to sag when the slide is tilted. In a personal communication a couple of years ago Dr. W. M. L. Coplin described to me a similar method he has used.

6. Duke's Modification of Milian's Method.—Duke's apparatus consists of a glass slide on which are mounted two 5 mm. disks. On one disk is placed a drop of the blood to be tested and on the other a drop of normal blood, the two drops being of about the same depth. The slide is then inverted over a tumbler nearly full of water kept at 40 C. and is covered with a warm damp cloth. When tested by tilting the cloth is removed and the slide taken up from the tumbler.

7. Author's Modification of Milian's Method.—Instead of a slide I use the lid of a German stender-dish, which I cover with the dish as soon as the drops are obtained. I measure the drops while covered and regard only the drops of proper size. Before the finger is punctured, and immediately after the drops are measured, the dish is placed in a pan of water, which is maintained at a constant temperature of 37 C. As the majority of my tests mentioned in this paper were made with this method I shall describe it in detail.

My coagulometer consists of a German stender-dish, 80 mm. in diameter and 40 mm. high, a pan big enough to hold the dish and fitted with an outlet tube and a bracket for supporting a thermometer, an ordinary bath-thermometer, a broad elastic band, a piece of rubber tubing, a clamp and a millimeter rule. I use an oval zinc pan, with perpendicular sides. As zinc is not acted on by water, it is preferred to tin, which rusts, and to copper, which turns green. (An ordinary five-cent tin baking-pan will answer, however, with an outlet and a bracket which a tinsmith will put in for ten cents.) The rubber tubing is attached to the outlet tube and clamped.

In employing this method, the under surface of the lid of the stender-dish is thoroughly cleansed with soap and water and then with alcohol, and dried. The rim of the dish is smeared with hydrated wool fat (lanolin) or petrolatum. The lid is then adjusted and held in place by the rubber band. The pan, with the thermometer in place, is partially filled with water of a temperature of 37 C (98 F.), that temperature being maintained by the addition of hot or cold water. Any excess of water is allowed to escape through the outlet. The dish is placed in the pan of water with the lid undermost.

The patient's finger is thoroughly cleansed with soap and water and with alcohol, and dried. The stender-dish is taken from the water and rapidly dried, and the elastic band is removed. A deep puncture with a sharp, lance-pointed instrument is made in the finger so that the blood flows freely without undue pressure. The first drop is wiped off and note is made of the exact time the second drop appears. When this drop reaches sufficient size it is touched to the uppermost surface of the inverted lid of the stender-dish, which is held horizontally, and deposited on it. The finger is again wiped off and several other drops are deposited similarly, the time of the appearance of each being noted. I usually take four drops, placing one in each quadrant, and mark the top of the lid with a pen or paraffin pencil. The dish is then placed on the lid and the diameter of the drops measured by passing the rule beneath the lid. It is best to disregard all drops whose diameters measure less than 5 mm or more than 8 mm. The rubber band is reapplied and the inverted dish is again placed in the water-bath.

At intervals the dish is removed from the water and tilted. At first this must be done cautiously to avoid the drops running; later the dish can be held vertically. The contour of the drop is observed from the side and the density is observed on full view. If, when seen from the side, the drop sags, becoming tear- or pear-shaped, or if, on holding the dish to transmitted light and looking at the face of the drop, it appears dense below and clearer above, complete coagulation has not occurred. But when the profile of the drop does not change when the dish is tipped vertically, but remains convex, and when the full view shows the density in the center or evenly distributed, the blood has fully clotted. To confirm this, the clot should be picked up or moved. Note is taken of the time at which this change occurs in each drop. The interval between the moment the drop appears on the finger and the moment it is completely coagulated is taken as the clotting time.

Twenty normal persons examined according to this method gave an average clotting-time of eight and two-thirds minutes with limits of twelve and one-quarter and four minutes.

2. *CLOTTING-TIMES ACCORDING TO THE DIFFERENT METHODS*

The length of time it takes a drop of blood to coagulate varies with the method employed for measuring it. In referring to a clotting-time, therefore, it is necessary to mention by what method it was obtained. The multiplicity of coagulometers, and hence of coagulation times, renders difficult any exact comparisons of results obtained by different observers.

I. THE NORMAL CLOTTING-TIMES ACCORDING TO THE DIFFERENT METHODS

In the following table are given the normal clotting-times obtained with the different methods by their originators. It will be seen that the greatest variations occur. There is practically no such thing as an absolutely normal clotting-time. In the same patient at the same time two minutes and twenty minutes may be the normal clotting-time, depending on the method employed.

TABLE 1.—NORMAL CLOTTING-TIMES OBTAINED WITH DIFFERENT METHODS

Method Employed.	Clotting Time Obtained
Vierordt's	9½ minutes
Wright's	2½ or 5 minutes
McGowan's	8 minutes
Addis' modification of McGowan's	9½ minutes
Rudolf's modification of McGowan's	8½ minutes
Sabrazés'	9 to 10 minutes
Schultz's	5 minutes
Brodie-Russell	3 to 8 minutes
Pratt-Grützner modification of Brodie-Russell	3 to 8 minutes
Bogg's modification of Brodie-Russell	3 to 8 minutes
Addis' modification of Brodie-Russell	8 minutes
Biffi's	7 to 10 minutes
Goldhorn's modification of Biffi's	about twice as long as above
Buckmaster's	5¾ minutes
Slide and Straw	2½ to 5 minutes
Schwab's	4¾ to 5½ minutes
Bürker's	6 to 7 minutes
Riebe's modification of Bürker's	12 to 14 minutes
Morawitz's	5 minutes
Hayem's	3 to 20 minutes
Milian's	15 to 34 minutes
Bezançon & Labbé's modification of Milian's	10 minutes
Hinman & Sladen's modification of Milian's	5 to 8 minutes
Duke's modification of Milian's	5 to 7 minutes
Author's modification of Milian's	8⅔ minutes

II. DEVICES FOR COMPARING PATHOLOGICAL CLOTTING-TIMES OBTAINED BY DIFFERENT METHODS

Owing to the wide variations in the normal clotting-times obtained with the different instruments, it is practically impossible to compare pathological records. This lack of uniformity is most unfortunate, as it prevents investigators from confirming each other's work. In order to overcome this difficulty I have devised two methods of comparing records taken with different instruments. With each apparatus one definite time must be taken as the normal. Where two figures are given, the mean should be taken.

1. Expressing the Pathological Clotting-Time in Terms of the Normal.—The clotting-time in a given disease may be expressed in terms of the normal by means of a fraction whose denominator is the normal time and whose numerator is the abnormal time; or this same fraction may be expressed as a decimal or as a percentage. Thus, if the normal clotting-

time obtained with one instrument is eight minutes and in a certain disease the clotting-time is six minutes, this latter may be expressed as 6-8, or 0.75, or 75 per cent. of the normal.

2. Reducing the Clotting-Time Obtained with One Method to the Terms of Another Method.—Another method of comparing records taken with different instruments is to reduce one to the terms of the other by means of proportion; i. e., the normal time of method A is to the normal time of method B, as the clotting-time in a certain disease taken with method A is to X, which is the abnormal time obtained by the A method expressed in terms of the B method. Thus, the abnormal time, six minutes, just referred to, would be expressed in terms of a method that gives the normal clotting-time as four minutes, by means of the following proportion:

Eight min. (normal time of first method): 4 min. (normal time of second method) ::6 min. (pathol. time according to first method) :X=3 minutes (pathol. time expressed in terms of second method).

3. FACTORS AFFECTING THE CLOTTING-TIME OF SHED BLOOD

The great variations in the clotting-time found by different observers, and even by the same observer, are doubtless due to factors of two kinds: intrinsic factors affecting the blood itself while still in the vessels, and extrinsic factors, affecting the blood after it has left the vessels.[1]

Of the factors affecting the clotting-time of shed blood, some doubtless have to do with the manner in which the blood is drawn, while others are connected with the method employed for measuring the clotting-time.

I. SOURCES OF ERROR IN THE METHOD EMPLOYED FOR MEASURING THE CLOTTING-TIME

The methods employed for measuring the clotting-time often themselves contain many sources of error. Some coagulometers are devised particularly to avoid certain of these factors. Undoubtedly there are causes of error that now are not even recognized.

1. Contact with Foreign Body.—Contact of the blood with anything except the intact endothelial lining of the vessel, oil, petrolatum or paraffin, shortens the clotting-time, the degree depending on the character and the size of the contact surface. Blood which Freund found to remain liquid when received in a greased vessel clotted when an ungreased glass rod was brought in contact with it. A portion of this blood, however, clotted in a few minutes when placed in an ungreased dish.

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1. The writer in September, 1908, presented a paper before the Medical Society of the State of Pennsylvania in which a number of these factors are described. Solis-Cohen, Myer: Factors Influencing the Coagulation Time of the Blood, Penn. State Med. Jour., 1909, xii, 953.

Addis made several tests showing the coagulation time to be seventy to eighty minutes when the blood was not in contact with a foreign body, twenty to twenty-six minutes when in contact with glass alone, ten to sixteen minutes when air was the only foreign body, and five minutes when the blood was exposed to both glass and air.

It is generally believed that uneven surfaces accelerate coagulation more than a surface of uniform character, such as smooth glass, and that with the latter contact surface, the greater its extent, the more rapidly coagulation occurs. That other factors may enter here is seen from the experiments of Bouchard, who demonstrated that when blood is received in a capillary tube, the portion of blood that enters the tube last coagulates more quickly than normal, while that portion that enters first clots more slowly than normal, this retardation being the greater, the longer the column of blood and consequently the greater the contact surface. It seems to him as if, in flowing through the tube, the blood divests itself of that which normally provokes coagulation, and as if that something accumulates in the first portion of the tube.

Whatever the amount of error due to contact with foreign bodies, it should always be constant in a given coagulometer. In each observation the blood should be in contact with exactly the same amount and kind of foreign body.

Capillary tubes offer the largest extent of contact surface. Vierordt's, Fox's and Koffmann's methods introduce second contact surfaces, a horse's hair in the first, water in the second, and the silver blade in the third. There are three foreign bodies in Mercier's method—the tube, the glass surface, and the rod, and two in Bürker's method—the water and the glass rod. McGowan breaks off the end of the tube containing the blood which entered first and consequently clots last, and then goes toward the portion which entered last and clots first. Sabrazès lessens this source of error by using a short tube, while Addis avoids it altogether by regarding only the last inch of blood.

In Hayem's method the extent of contact surface is large and, besides, many drops fall on the sides of the test-tube. The needle, or straw, and slide introduce two foreign bodies into the method employing them. Wire loops present an uneven surface; Goldhorn notes that in Biffi's instrument the blood goes by capillarity to the point where the two wires cross. The contact surface is smallest in the Brodie-Russell method and its modifications, in Milian's method and its modifications, and in Schwab's hanging drop.

2. Dirt.—The clotting-time is affected by the presence of dirt, no matter how minute, on the contact surfaces and on the finger. Absolute cleanliness of skin and instruments is essential.

Capillary tubes, especially if beaded, and wire loops are not so easily cleansed as are glass slides, the lid of a stender-dish, and the smooth surface of a glass cone.

3. Size and Shape of Drop.—Hartman, Bezançon and Labbé, and Hinman and Sladen believe that the size of the drop has some influence on the clotting-time, but Bürker thinks not. Addis states that if the margin of the drop does not come absolutely up to the edge of the surface of the cone of the Brodie-Russell instrument, the stream of oil will not affect it in quite the same way; again, that the drop is then not always circular in outline, and the flow of corpuscles is liable thereby to be slightly obstructed.

In my method I found that the size of the diameter of the drop affects the coagulation time very little, provided it is not less than 4 mm. or greater than 7 mm. Often the clotting-time was the same in drops whose diameter measured 4 mm. at one extreme and 8 or 9 mm. at the other, obtained from the same puncture and examined at the same time.

The diameter of the drop is uniform in size in Hinman and Sladen's, Schwarz and Ottenberg's, Duke's, and my modifications of Milian's method.

It must be borne in mind, however, that the diameter of a drop is not always an accurate index to the amount of blood contained in the drop. The height must also be taken into account.

In thirty-five cases (of tuberculosis) where the drops were high, the average coagulation-time was five and three-quarter minutes. In fifteen tests with shallow drops the average time was only four minutes. According to Duke, also, a very shallow drop clots one to two minutes sooner than a very deep one.

There seems to be some relation between the size of the drop and the viscosity of the blood. This may be due to the fact that the viscid drops are always high; while, on the other hand, when the viscosity is low, the drop tends to spread and thereby becomes shallow. On this account my drops of large diameter were usually very shallow. The longer clotting-time of high drops may, however, also be explained by their increased viscosity.

I always endeavored to obtain high drops.

The difference that others have noticed in the clotting-time of drops of different sizes may be in part a result of the quicker evaporation of the smaller drops; while the fact that drying is less likely to occur when the drops are protected by the stender-dish, may account for my results.

Another factor, related to the height of the drop, demonstrates the importance of viewing the drop from the front as well as from the side, when examining drops according to Milian's method or one of its modifications. A high drop ceases to change its shape when tilted and

observed from the side before the density ceases to change when the tilted drop is looked at in front. The reverse is true of shallow drops.

4. Amount of Blood Withdrawn.—As will be shown later, there is a tendency for the coagulation-time of the blood to diminish during and after a hemorrhage. It is important therefore not to withdraw enough blood to produce this reaction. The methods that use but a few drops of blood seem to me preferable. Hayem's method of filling a test-tube with blood is therefore not a fair test. This progressive diminution of the clotting-time is fairly rapid. In one of Addis' cases, the first blood from the wound clotted in seven and one-quarter minutes, that obtained after one minute in five and one-quarter minutes, and blood flowing after two minutes in three and three-quarter minutes. The blood introduced in the last of a series of capillary tubes would therefore coagulate more quickly than the blood in the first tubes. Even in a small capillary hemorrhage of a few drops there seems to be a slight difference in the coagulability of the different drops. In my tests with my method each drop clotted about one-eighth or one-quarter of a minute quicker than the drop immediately preceding. This of course may have been more apparent than real. It merely means that the moment coagulation was noted as being complete all the four drops were usually well clotted, although they had been obtained one-eighth or one-quarter of a minute apart. It is no doubt possible that in some instances the exact moment in which clotting occurred in each drop was not immediately noted, as the drops were observed only at intervals. In many cases, however, the drops were examined at the very instant coagulation was taking place.

5. Mechanical Disturbance of the Blood.—It is probable that coagulation is hastened by any disturbance of the blood, such as pulling a horsehair through it, as in Vierordt's method, or trailing a needle, wire, glass rod, or straw, through it, as in several methods, or tilting the drop, as in Hayem's, Buckmaster's, and Milian's method and its modifications, or setting it in motion by a current of air or oil, as in the Brodie-Russell instrument and its modifications, or in whirling it against a blade, as in Koffmann's coagulo-viscosimeter.

6. Evaporation.—Milian has shown that evaporation, by diminishing the quantity of water in the blood, accelerates coagulation. Hence currents of air interfere with the test.

In the first tests I made with the uncovered slide, according to Milian's method, the evaporation of the blood was quite marked; by the time coagulation was complete, the drops were dried about the edge for a third of their diameters. My recent comparative tests made simultaneously with covered and uncovered drops of blood from the same person, would seem to indicate some relationship between evaporation and the

humidity of the air. In blood exposed to the air, coagulation was seven-eighths of a minute longer when the humidity was 75 or above than when it was below 75.

In Milian's method, as well as in Hinman and Sladen's modification of it and in the methods in which one drop or several drops of blood are collected on a slide and tested with a needle, wire, or straw, the blood is exposed to the air and consequently to evaporation. Those methods therefore can be used only in a closed room. In Bezançon and Labbé's and Duke's modifications of Milian's method the slide is exposed to the air whenever it is examined. The thin film used by Buckmaster and Biffi surely must have a tendency to evaporate. Air is definitely blown on the drop of blood in the Brodie-Russell apparatus and in the Pratt-Grützner and Boggs modifications of it, the force and frequency of this disturbing feature naturally varying with the operator. The blood is protected from drafts in Schwarz and Ottenberg's and my modifications of Milian's method and in the methods employing capillary tubes, which therefore can be used in a ventilated ward, or in the open air in the case of consumptive or pneumonia patients.

7. *The Temperature.*—Pratt, Murphy and Gould, McGowan, and Hinman and Sladen are of the opinion that coagulation is not appreciably affected by moderate variations in the temperature, but present no experimental proof of this assumption. Milian, Bürker, Bezançon and Labbé, Goldhorn, Denk and Hellman, Weil, and Jacquot, on the other hand, assert that heat accelerates coagulation, while cold retards it. This action has definitely been shown experimentally to be a fact by Addis, Brodie and Russell, Fox, Hartman, Rudolf, Wright and myself.

Wright found the clotting-time to be two to four minutes when his tubes were kept at 18.5 C., and one minute and thirty-five seconds to two minutes and ten seconds when the water registered 37 C. Brodie and Russell obtained a clotting-time of eight and eight and a quarter minutes when the water in the instrument was 20 C., and three to four minutes with a temperature of 30 C. Rudolf's figures show that, roughly speaking, each degree between 15 and 20 C. of the temperature at which the test is carried out makes a difference of about one minute in the coagulation-time.

Addis constructed a chart showing a regular decrease in the clotting-time from two and one-half minutes at 10.25 C. to five and one-half minutes at 20.5 C. This writer regards as practically worthless methods where no attention is paid to differences of temperature. He believes the extraordinary variations in coagulation-times obtained by use of these methods to be to a great extent due to variations of the temperature.

My own experiments also demonstrate that temperature does exert an influence. Five comparative tests were made at the same time with blood

from the same persons, kept both at 37 C. and at 18.5 C. The average clotting-time in four of these cases was six and three-quarter minutes at the higher temperature and eight and one-quarter minutes at the lower. The fifth case gave a clotting-time of eight and one-quarter minutes at 37 C. and of twenty and three-quarter minutes at 18.5 C., the latter probably being a result of the condensation of moisture on the inside of the dish.

A series of observations was also made on blood from the same persons tested both with the author's method at a temperature of 98 F. and on an uncovered glass slide at room temperature. Five subjects were tested when the room temperature was 75 F. and above, and twelve subjects were tested when the room temperature was below 75 F., with the results shown in Table 2.

TABLE 2.—INFLUENCE OF TEMPERATURE ON THE CLOTTING-TIME

	Blood from the Same Persons Tested Simultaneously According to:			
	Writer's Method at 98° F.	Milian's Method at 75° F. and above	Writer's Method at 98° F.	Milian's Method at a Temp. Below 75° F.
Number of cases	5	5	12	12
Aver. Clotting Time	9⅜′	9¾′	9⅕′	10½′
Max. Clotting Time	10¼′	11⅜′	12¼′	14¾′
Min. Clotting Time	8¼′	6⅝′	3¼′	3′

Blood kept at 98 F. therefore took five-eighths of a minute longer to clot than blood exposed to a room temperature of 75 F. or more, but one and three-tenths minutes less than blood exposed to a room temperature below 75 F.

On hot days, in order to keep the water in the pan at 18.5 C., ice-water had to be added continually. In such cases there was always a little moisture condensed on the top or sides of the dish, and on very hot days so great a condensation appeared on the lid that it constituted an additional element of error. When, for instance, the room temperature was 90 F., drops on an uncovered slide clotted in less than eight minutes, and those in a stender-dish kept at 37 C. (98 F.) coagulated in eight and one-quarter minutes, but it was twenty and three-quarter minutes before clotting occurred in the drops that were tested in a stender-dish at a temperature of 18.5 C. (66 F.).

There is no doubt that the adhesion of the blood to the glass contact surface is affected by temperature. Whenever the glass is not heated to 98 there is a great tendency for the drop to run when tilted. The blood adheres much better when the glass surface is kept at the higher temperature.

A drop tends to spread when deposited on a cool glass surface, and, being shallow, clots more quickly than a similar drop deposited on a warm surface, where it remains high.

Coagulometers that seem to keep the blood at a constant temperature vary in the thoroughness with which they accomplish this. Denk and Hellman point out an error in the gauge of the capillary tubes, stating that the thickness of the glass affects the rapidity of warming and emphasizing the need of very thin tubes. According to this, Wright's home-made tubes are more accurate than those supplied by the instrument-maker. The stender-dish I use is of rather thick glass.

In Sabrazès' method, in Addis' modification of McGowan's method, and in my own method the tube or dish containing the blood is removed from the water to be tested, during which time its temperature tends to approximate the room temperature. Addis has recently stated that further experience with his modification of McGowan's method has shown that the results cannot be relied on if the room temperature is above 20 C. (68 F.). Coagulation-times taken on hot summer days when the temperature in the ward was above 20 C. were found to be shorter than normal, although the temperature within the apparatus was kept at 20 C. The higher temperature outside, according to Addis, must therefore have accelerated the coagulation, although it had an opportunity to act only during the relatively short time during which the tubes were removed from the apparatus for examination. A large part of the difference in the coagulation times of people in health, he thinks, was no doubt due to this cause.

Addis found it impossible to maintain a constant temperature in Brodie-Russell's, Bürker's, and Buckmaster's instruments. There seems to be little doubt that Addis' modification of the Brodie-Russell instrument and Wright's coagulometer maintain an uninterrupted constant temperature.

8. Dilution of the Drop.—Bürker states that the dilution of drops of blood had no influence on the coagulation-time. Stodel, however, demonstrated that blood diluted with a solution of sodium chlorid 9 to 1,000 coagulated more slowly than pure blood, and also that the greater the dilution the more slowly coagulation occurred.

9. End-Point Adopted.—The end-point adopted in the different methods as indicating that coagulation has occurred is not always accurate, clear and definite. The methods employing capillary tubes, as well as those in which the blood is watched for the appearance of fibrin threads, have practically the same end-point. According to the investigations of Addis, Buckmaster, Fox, and others, this is not sure proof that coagulation has occurred in the whole drop, as a thread of fibrin several millimeters long can often be demonstrated ten seconds after the blood has

been drawn, when the blood is touched with a needle or with a glass surface. In such a case there are no other signs of coagulation and the same drop may give a coagulation time of seven or eight minutes. The conditions under which this phenomenon occurs are present when the blood is blown out of one of Wright's tubes and the tube is slowly withdrawn from the drop, and are always present in Mercier's method.

Those methods having as an end-point a loss in fluidity, as Hayem's, Brodie and Russell's and its modifications, Milian's and its modifications, and Buckmaster's, are subject to a source of error in that the change in the physical character of the blood may be due to agglutination of the corpuscles.

In Brodie and Russell's method and its modifications the end-point is not always the same in the hands of different observers. Addis mentions three possible stages, sixty and fifty seconds apart, which might be adopted as indicating coagulation. Hinman and Sladen divide into four stages the changes in the movement of the red corpuscles set up by the blowing. They believe that Pratt and Murphy and Gould adopted as an end-point the stage they label C, while Brodie and Russell used stage D, the stage Hinman and Sladen finally used themselves.

10. Personal Equation.—I regard the personal equation as a very important factor. To it I attribute largely the fairly constant results obtained by each investigator with the instrument he has devised or is accustomed to, when others obtain discordant results with the same method. Whatever the factors of error, they usually remain about the same when the test is always performed in exactly the same manner. Familiarity with a method and facility in its employment even lessen the effects of sources of error connected with it. In Milian's method and its modifications, for instance, that man will disturb the drop least who needs to tilt the drop least often and who can observe its shape most quickly. As already mentioned, the determination of the end-point in several of the methods, particularly Brodie and Russell's, is often a matter of personal equation. In the latter method the force and frequency with which the bulb is compressed, affecting two factors—the draft of air and the mechanical disturbance of the drop, depend on the individual compressing it. The manner of obtaining the drop of blood and the rapidity with which it is transferred to the apparatus undoubtedly varies with different workers.

Complicated methods, and those requiring technical skill, experience, and powers of observation of a high order, are most likely to be affected by the personal equation. A coagulometer, to be reliable, must give the same kind of results in everyone's hands.

11. Unrecognized Causes of Error.—There are many sources of error not recognized at present. These probably explain the curious results

that are sometimes encountered. The coagulometers that always give constant results under the same circumstances are probably freest from the unrecognized factors of error.

With my method results are fairly constant. Four drops taken in succession from the same puncture usually coagulate in about the same periods of time. The results obtained from two different punctures, made fifteen to thirty minutes apart, are as a rule fairly constant. This probably means that unrecognized sources of error have been reduced to a minimum.

Hayem's method gave unsatisfactory and discordant results in his own hands, the time varying greatly in one and the same animal.

My own results with Wright's tubes were unsatisfactory. It was often my experience that the blood in eight tubes filled from the same puncture did not coagulate in equal periods of time. Wright's method proved unsatisfactory in Brodie and Russell's hands, successive observations taken at intervals of five to ten minutes not giving concordant results. In the hands of Murphy and Gould it failed to give results in 15 per cent. of the observations. In a certain number of cases the blood would not adhere to the lumen of the tube, a fact they were unable to explain. They found in blood from healthy subjects variations between one and seven minutes, which extremes they attribute to technical errors. Turner, using Wright's tubes, often found a difference of over two minutes in the blood from three successive pricks in the same individual on different fingers; on only three occasions in over 1,000 observations did he find the same coagulation rate in the blood from three consecutive pricks. In nearly 50 per cent. of the forty-three estimations made by Addis with Wright's tubes, only an approximate time could be arrived at, because coagulation occurred in one tube although it was not present in others until later.

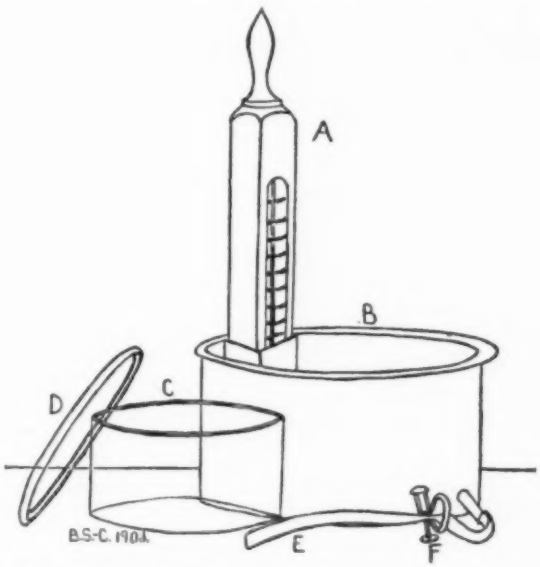
The Brodie-Russell instrument failed in less than 5 per cent. of the observations in Murphy and Gould's hands, but it gave variations in blood from healthy subjects between one and seven minutes. Pratt noted extraordinary variations in the coagulation-time taken with his modification of this instrument, the time in one case varying from two to nine and one-half minutes within half an hour. Addis in over 200 estimations with Pratt's or Bogg's modification of the Brodie-Russell coagulometer, found that with its use the time varied considerably in consecutive observations on the same person, a time of four minutes being followed by one of twelve minutes, and so on, without any regularity.

Bezançon and Labbé found inexplicable variations in their modification of Milian's method, sometimes the first drop, sometimes the last drop coagulating most quickly. Hinman and Sladen found their modification of Milian's method to be thoroughly reliable. In my hands also it has given satisfactory results.

II. COMPARISON OF THE DIFFERENT COAGULOMETERS

The methods of measuring the coagulation time that are freest from sources of error are Addis' modification of Brodie and Russell's method and my modification of Milian's method. The former is probably the most accurate of all, but is too intricate and cumbersome for general application, being fitted chiefly for laboratory use.

My coagulometer seems to me to combine simplicity with accuracy. It can be made and used by any physician and is easily carried about. At the same time it presents a contact surface limited in extent, clean, and uniform in character, maintains a fairly definite and constant tem-



Author's Congulometer; A, ordinary bath thermometer; B, zinc pan (common tin pan will answer): C, German stender-dish; D, lid of German stender-dish; E, rubber tube; F, clamp.

perature, prevents evaporation, provides for drops of uniform size, largely eliminates the personal equation, and presents fairly constant results.

While less accurate than the above, Milian's method is the simplest of all, requiring merely a plain glass slide. It is always available and as a rough test is to be recommended.

III. FACTORS DEPENDING ON THE MANNER THE BLOOD IS DRAWN

There are some conditions affecting the coagulation of shed blood which are not produced by the instruments used but have to do with the manner in which the blood is drawn.

1. The Part Punctured.—Murphy and Gould found no marked difference between the coagulation times of blood drops taken from different points on the surface of the body, provided the flow had been equally free. It was Pratt's experience also that there were no characteristic differences in the coagulation time dependent on the part examined, although he remarks that blood from different parts of the same individual, examined at the same time, showed striking differences in the coagulation time. Hayem, on the other hand, using his own method in simultaneous observations, obtained clotting-times of nine minutes in blood from the ear and two minutes in blood from the thigh.

2. Contact with the Tissues.—That contact with the tissues shortens the clotting-time has been noted by many observers, some of whom variously attribute this influence specifically to the wound, the blood, lymph, and the skin.

It is the coagulant action of the tissues which, according to Delezenne, causes immediate clotting of blood at the surface of the wound. Spangaro also has shown that blood taken directly from a vessel takes a much longer time to clot than when it first comes in contact with the tissues. Coagulation was equally hastened when a small portion of muscle or glandular tissue was introduced into the tube where the blood was received directly from the vessel or when the sides of the tube were merely rubbed with the tissues.

A. Influence of the Wound: Delezenne showed that bird's blood clots in half a minute to two minutes when allowed to come in contact with the wound, but remains unclotted for two to eight days when drawn directly from the vessel through a glass tube.

Arthus showed in dogs that the coagulation of blood flowing on the wound was always more rapid than that of blood received in a tube—forty seconds, for example, instead of three minutes. By allowing a 1 to 100 sodium chlorid solution to fall drop by drop on the surface of an exsanguinated cutaneous wound he obtained a saline lavage water capable of hastening coagulation of the blood. Making the lavage water flow over the wound several times in succession increased its coagulating power.

Milian and Addis believe that fibrin ferment quickly forms and collects around the lips of the wound, and tends to shorten the coagulation-time of the blood which follows. Spangaro states that when a portion of tissue is placed in blood obtained without contact with the tissues coagulation is not so rapid as when the blood comes in direct contact with the wound.

Mellanby gives a detailed theoretical explanation, stating that when a blood-vessel is so injured that blood may escape from it, the injured vessel-wall or the surrounding tissues liberate kinase. This kinase enters

into the blood and there finds all the necessary factors for the production of fibrin ferment—prothrombin and calcium salts. Fibrin ferment is therefore formed and since the association of the prothrombin with the fibrinogen entails that the ferment produced is in molecular proximity to the fibrinogen, coagulation of the fibrinogen ensues in the shortest possible time.

Bernheim very recently demonstrated experimentally that in the blood-vessel wall itself there is a substance which, once the vessel is injured, probably aids in the formation of a clot.

B. Contact with Blood: When the drop to be tested comes in contact with recently shed blood a very marked diminution in the clotting-time results. Addis attributes this to the addition to freshly issuing blood of preformed fibrin ferment. Spangaro has shown that contaminating the sides of a tube with blood hastens the coagulation of blood that is received into it without having come into contact with the tissues.

In drawing blood for testing, therefore, it is absolutely essential that all trace of one drop be removed before the next appears.

C. Contact with Lymph: Wright pointed out the influence of lymph in decreasing the clotting-time, as shown by the admixture of blood to fresh lymph, muscle juice, and blister fluid. The acceleration of coagulation when pressure is made on the tissues he attributes to the driving of lymph into a bleeding wound, and contrasts the short coagulation-time of the "mixture of blood and lymph obtained from a small occluded puncture on the finger" with the much longer coagulation-time of the blood issuing spontaneously from a free puncture. The effects of the wound and of blood he believes to be due to the admixture of lymph contained by blood leaving a wound.

Pratt has found that an increased amount of lymph in the tissues does not accelerate the coagulation-time, blood from very edematous tissues not coagulating more rapidly than blood from non-edematous parts of the body.

D. Influence of the Skin: Milian believes that there exist in the skin substances that accelerate coagulation. Hinman and Sladen found that the longer a drop is in contact with the skin surface, the more rapidly it clots when transferred to the instrument, each second of contact added shortening the coagulation-time by minutes. They also state that the more rough and scaly the skin, the quicker is the normal clotting. Addis compared the coagulation-time taken when the blood was protected from contact with the skin by smearing the surface with hydrated wool fat (lanolin) before the puncture was made, with the time taken in the ordinary way. This showed that contact with the skin for the short period which elapses before the blood can be introduced into the apparatus has no appreciable effect.

It is quite possible (if not probable) that the influence supposed to be exerted on the clotting-time by contact with the wound, the skin, blood and lymph, are all due to one and the same factor, the action of fibrin ferment which, as Mellanby has stated, does not circulate in the blood, but is produced when any tissue is injured so as to liberate thrombokinase in the blood-stream.

3. Depth and Character of the Wound.—Pratt found the clotting-time to be influenced by the depth and extent of the cut. If a large, deep cut were made, from which the blood flowed freely, the coagulation-time was relatively slow, while blood from a small superficial cut coagulated quickly. In one case, for instance, blood from a superficial cut of the skin coagulated in two minutes, while blood from a deep cut in the same individual coagulated in seven minutes. Murphy and Gould furnish an explanation of this phenomenon, stating that if the needle-prick is deep, the rapid flow of blood will wash away the ferment and prevent immediate coagulation, while the reverse is true of a superficial prick. They regard it as obvious that the prick should be deep enough to cause a free flow of blood. The accelerated coagulation of blood from a superficial puncture Hinman and Sladen attribute to the longer contact of the blood with the skin, owing to its slow and scanty flow.

On the other hand, Addis has found that there is no appreciable difference in the coagulation of blood from deep and superficial punctures. In eight comparative observations the average time from deep punctures was eight minutes, eight seconds, and from superficial punctures, eight minutes, four seconds. It has been my experience also, that, provided the puncture is fairly good and made with a sharp, lance-pointed instrument, it introduces no element of error.

4. Rate of the Flow.—The rate of flow of blood from the wound, provided it is fairly free, does not affect the clotting-time, according to my experience. Addis, however, states that the rate of flow has proved to be of importance in so far as it affects the time during which the blood is exposed to the air before its introduction into the apparatus. He believes air to have a marked influence on coagulation: its temperature is variable, and dust particles no doubt attach themselves to the drop to a variable extent during its exposure to the air. In a more recent article he states that the amount of thrombokinase, which is one of the most important factors determining the coagulation-time in the blood flowing from a wound, is mainly determined by the length of time during which it has been in contact with the exposed tissues in the wound. Too long contact with the skin, according to Hinman and Sladen, is the element of error in a slow and scanty flow. In one of their cases there was a clotting-time of twenty-three and one-half minutes when there was a freely-flowing hemorrhage and eighteen and three-quarters minutes when

the flow from a second puncture was scanty. At another time with free rapid flow, the time was twenty-two minutes; with comparatively slow flow, fifteen minutes. Murphy and Gould, as mentioned before, attribute the longer coagulation when the flow is free to a washing away of the ferment. As a rule the rate of flow depends on the depth of the puncture.

5. Pressure on the Part.—Pressure on the parts in expressing the blood introduces a factor of some importance in proportion to the degree of pressure exerted. In ten normal persons blood obtained without any pressure and tested with my coagulometer clotted in eight and seven-tenth minutes. In six cases in which but slight pressure was exerted the coagulation-time was seven and one-half minutes, and in four instances in which the pressure was more marked the time was six minutes. The same was true of tuberculous patients (whose average clotting-time in 100 cases was five and one-sixth minutes). The average coagulation-time of ten patients with no pressure was six and one-eighth minutes, of twenty patients with slight pressure four and seven-eighths minutes, of twenty-six patients with greater pressure four and one-quarter minutes. In no case was much pressure exerted.

Wright, Milian, and Pratt also found the clotting-time shortened by pressure on the tissues, Wright attributing it to the driving of lymph into a bleeding wound. Addis, on the contrary, was not able to find that pressure makes any appreciable difference, the average time he obtained with pressure being eight minutes, five seconds, and without pressure eight minutes, four and three-quarter seconds.

6. Stage of the Hemorrhage.—That the last-drawn blood clots more quickly than that drawn first is stated by Hewson, Nasse, Brücke, Arloing, von der Velden, Cohnheim, Arthus, Bezançon and Labbé, Pratt, and Addis. This refers to both large and small hemorrhages, being more marked in the former. Milian, and Hinman and Sladen state that drops at the beginning or end of a hemorrhage clot more rapidly than those in the middle; the last believes this to be due to the different rate of flow, an evidence of the influence of skin contact.

Addis was able to demonstrate that a rapid and progressive diminution of the coagulation-time occurs as the hemorrhage continues. Thus the first blood to appear from a wound clotted in seven minutes, fifteen seconds; blood flowing from the wound after one minute in five minutes, fifteen seconds; after two minutes in three minutes, forty seconds. He attributes this change to the influence of fibrin ferment in the wound. Pratt, however, found that a second drop of blood obtained from a cut after the first has coagulated always coagulates more rapidly than the first, even when the skin, after the removal of the first drop, is cleansed carefully with water, alcohol, and ether. Rudolf similarly found that at 20 C. the blood from the first drop coagulated in nine minutes, and that

from the same wound two minutes later in five minutes and forty-five seconds, the wound having been carefully wiped dry and clean before the second drop was taken. On another occasion, under similar circumstances, the respective readings were eight and five minutes for the first and second drops at a two-minute interval.

7. *Congestion of the Part Punctured.*—Several observers, in objecting to constricting the finger before drawing blood from it, state that congestion of the part from which the blood is obtained leads to diminution in the clotting-time, the explanation being that a greater quantity of coagulation-accelerating substances from the tissues is added to the blood. Wright states that venous congestion by ligatures increases coagulability, believing it due to the effect of carbon dioxid.

Addis found no such change. He produced a very marked congestion in one arm by the application of a Bier's bandage above the elbow. The average of twelve comparative estimations of the clotting-time of blood taken from the congested fingers was eight minutes, two seconds, while the average time of blood taken from the uncongested fingers was seven minutes, fifty-one seconds.

4. *INTRINSIC FACTORS, PROBABLY AFFECTING THE BLOOD WITHIN THE VESSELS*

In addition to errors in technic that affect the clotting-time of drawn blood, there are probably other factors that may influence the coagulability of the blood while still in the vessels. These include external influences; conditions of the body, normal and pathological; and substances introduced into the body from without.

I. EXTERNAL CONDITIONS (METEOROLOGICAL)

In many instances I made note of the meteorological conditions existing at the time the test was made, including temperature, barometric pressure, humidity and sunshine.

1. *Outside Temperature.*—The clotting-time apparently does not vary with the outside temperature. I noted the outside temperature when making many of my tests, and have grouped the normal and non-tuberculous and also the tuberculous cases according to whether the outside temperature on the day of the test was above or below 75 F., and in the tuberculous cases also above or below 80 F.

It was noted by Robertson and his assistants that the temperature and humidity of the atmosphere influenced the coagulation-time noticeably and uniformly, a hot day with heavy atmosphere causing the coagulation-time to shorten, while a cool day had the opposite effect. Before I had compiled my figures I had the same impression, and thought that possibly

the low average time of the 100 cases of tuberculosis I examined (five and one-sixth minutes) might have been due in part to the fact that most of the tests were made during the hot months of July and August.

TABLE 3.—CLOTTING-TIME AT DIFFERENT TEMPERATURES

(Obtained with author's coagulometer.)

	Normal and Non-Tuberculous Cases at a Temperature of		Cases of Tuberculosis at Temperatures of			
	75° F. and Above	Below 75° F.	80° F. and Above	Below 80° F.	Above 75° F.	75° F. and Below
Number of cases	14	25	55	45	81	19
Number of observations	14	30	72	57	99	28
Av. clotting-time (minutes)	8	7⅞	5 1/7	5¼	5 2/5	5
Max. clotting-time (minutes)	12¼	12¼	10⅜	10⅜	10⅜	7⅞
Min. clotting-time (minutes)	4⅝	3½	2¼	2⅛	2¼	2⅛

2. Humidity.—There is apparently no definite relationship between the humidity and the clotting-time. I made note of the humidity on the day of the test, but found it exercised very little influence. The results, in fact, were slightly at variance in thirty-nine normal and non-tuberculous cases and in ninety-seven tuberculous cases.

TABLE 4.—CLOTTING-TIME AT DIFFERENT DEGREES OF HUMIDITY

	Normal and Non-Tuberculous Cases With a Humidity of		—Tuberculous Cases With a— Humidity of			
	75 and Above	Below 75	75 and Above	Below 75	70 and Above	Below 70
No. of cases	19	20	33	64	55	41
No. of observations	21	23	39	86	71	55
Av. clotting-time (minutes)	7 4/5	8	5½	5	5½	4⅞
Max. clotting-time (minutes)	12¼	12¼	10⅛	10⅜	10⅜	10⅜
Min. clotting-time (minutes)	4	3½	2¼	2⅛	2¼	2⅛

Robertson and his assistants, as mentioned above, thought that humidity did affect the clotting-time.

3. Barometric Pressure.—The clotting-time in normal and non-tuberculous individuals seemed to be influenced by the barometric pressure, being shorter by two minutes when the barometric pressure was below 30.1 than when it was 30.1 or above. In the tuberculous cases, however, no difference was observed.

TABLE 5.—CLOTTING-TIME AT DIFFERENT BAROMETER PRESSURES

	Non-Tuberculous Cases; at a Barometric Pressure of		Tuberculous Cases; at a Barometric Pressure of	
	30.1 and Above	Below 30.1	30.1 and Above	Below 30.1
No. of cases	30	14	41	56
No. of observations	30	18	52	74
Aver. clotting-time (minutes)	8⅜	6½	5 1/5	5 1/5
Max. clotting-time (minutes)	12¼	10⅛	10⅜	10⅜
Min. clotting-time (minutes)	3½	3⅞	2⅛	2¼

4. Amount of Sunshine.—Note was made of the number of hours of sunshine on the day of the test in ninety-seven cases of tuberculosis. On the days when there were more than eleven hours of sunshine the clotting-time was half a minute longer than on days when the hours of sunshine were eleven or less.

TABLE 6.—RELATION OF THE CLOTTING-TIME TO THE AMOUNT OF SUNSHINE

	Cases of Tuberculosis	
	11 Hours of Sunshine or Less	Over 11 Hours of Sunshine
Number of cases	45	52
No. of observations	52	72
Aver. clotting-time (minutes)	5⁹/₁₀	4⁹/₁₀
Max. clotting-time (minutes)	10⅜	7¾
Min. clotting-time (minutes)	2⅛	2¼

II. CONDITIONS AFFECTING THE BLOOD ITSELF

There are a number of conditions within the body itself that exert some influence on the clotting-time. Several affect the blood directly, while others have an effect on the body as a whole.

1. Viscosity.—Buckmaster states that the viscosity of the blood as determined by Hürthle for animals and Hirsch and Buck for man, is found to be inversely related to the coagulation-time, and that the less the viscosity the greater the time. In Addis' cases, however, no relation appeared to exist between the viscosity of the blood and its coagulation-time. Delayed, normal and accelerated coagulation-times were all observed in different cases where there was undoubtedly an increase or decrease of viscosity. Addis thinks the belief that there is a connection between viscosity and coagulation is due to the fact that, unless special precautions are taken, when the blood has an increased viscosity, it takes a longer time than usual to flow from a wound, and takes up more thrombokinase, and so gives a shorter time than normal blood or blood in which the viscosity is low. In my own cases the clotting-time was longer in the viscid than in the non-viscid drops, as may be seen from Table 7.

TABLE 7.—RELATION OF THE CLOTTING-TIME TO THE VISCOSITY

	Normal Cases		Tuberculous Cases	
	Viscid	Not Viscid	Viscid	Not Viscid
Number of cases	8	5	35	21
Number of observations	8	5	37	22
Aver. clotting-time (minutes)	10	8⅞	5⅜	5¼

This longer clotting-time of viscid drops may be due to the fact that viscid drops are deeper or higher than drops of low viscidity having the same diameters, and consequently contain more blood. The drop of low viscosity, being shallow, is therefore more likely to evaporate and to become dry around the edges than the more viscid and consequently

higher drop. That there is a marked difference between the clotting-times of high and shallow drops, amounting to one and three-quarter minutes, Table 8 shows:

TABLE 8.—RELATION OF HEIGHT OF DROP TO CLOTTING-TIME

Cases of Tuberculosis	High Drops	Shallow Drops
No. of cases	35	15
No. of observations	36	15
Aver. clotting-time (minutes)	5¾	4

It was my experience, moreover, that a viscid drop when tilted may sometimes retain its convex shape before it is completely coagulated. Consequently in Milian's method and its modifications a high degree of viscosity may constitute a source of error. It also has seemed to me that viscid blood sticks to glass better than does thin blood. Should this be the case, viscidity may interfere to some extent with the accuracy of some of the instruments used, such as those of the Brodie-Russell type and particularly those employing capillary tubes.

According to Coleman, altered viscosity may introduce a fallacy in the Brodie-Russell instrument that is difficult to remove. When there is a considerable diminution of the surface tension of the blood, the size of the pendulous drop is much less and therefore the blood is exposed to a relatively large surface of glass, and consequently the observed coagulation-time is unduly shortened.

In my tests the viscosity was judged as being high or low in accordance with the appearance or behavior of the drop. A series of comparative observations on cases in which the viscosity is accurately measured with an instrument of precision might prove of value.

2. Blood-Pressure.—Hartman states that a variable blood-pressure has no influence on the clotting-time.

3. Agglutination.—In healthy persons variations in the agglutination of red blood-cells are slight, according to Addis, and have never given rise to serious error or difficulty in tests made with his modification of the Brodie-Russell instrument. In disease the agglutination of corpuscles is greatly increased and in some convalescents it is present in varying degree, preventing estimation of the coagulation-time with his instrument in many cases.

4. Hemoglobin.—The amount of hemoglobin apparently has no relation to the clotting-time. Of twenty-three cases of anemia I tested with Wright's coagulometer at 37 C., sixteen with between 50 and 75 per cent. of hemoglobin had an average clotting-time of two and one-half minutes (normal) and five with hemoglobin below 50 per cent. had an average time of two and five-sevenths minutes. Schwab also states that no relation exists between coagulation and hemoglobin, an exsanguinated patient with carcinoma, with scarcely 10 per cent. hemoglobin, having the same clotting-time as another person with 70 or 90 per cent.

5. Leukocytes.—It is the view of many that a high leukocytosis increases coagulation. Stessano and Billon attempt to show by experiments that the blood's content of fibrin ferment is in proportion to the number of leukocytes it contains. Arthus and Milian both regard fibrin ferment as the product of the secretion of the white blood-cells. Stessano has advanced the hypothesis that of the different kinds of leukocytes the mononuclears are more particularly concerned in caring for the elaboration of fibrin ferment. He thinks, moreover, that the fact that lymph coagulates spontaneously proves that the mononuclear leukocytes, which are the only elements normally figuring in lymph, are well capable of setting free fibrin ferment. In Addis' cases, on the other hand, no evidence was obtained of any connection between leukocytosis and coagulability. All varieties of coagulability were seen, in cases both with and without leukocytosis.

Duncan says too that in cases of high leukocytosis, as in pneumonia, he could not determine that the coagulation-time was hastened. According to Coleman, however, when leukocytosis occurs, either as the result of some pathological condition or of the hypodermic injection of a drug, lengthening of the clotting-time of the blood accompanies it.

No definite relationship could be made out in my cases between the clotting-time and the total number of leukocytes or of the number of mononuclear cells. In thirty-three cases (excluding those of pneumonia) in which the clotting-time was two and one-half minutes, or longer, as determined with Wright's coagulometer at 37 C., the average number of leukocytes was 8,671. In forty-three cases (excluding pneumonia) in which the clotting-time was less than two minutes, the leukocytes averaged 8,176. Adding two cases of pneumonia to the former group and fifteen cases of pneumonia to the latter group brings the average number of leukocytes in these groups up to 8,994 and 14,017 respectively. In one case of pneumonia the clotting-time was estimated six times during the course of the disease. The average clotting-time of the first three examinations, made when the leukocytes averaged 50,653, was two minutes, ten seconds; the average time of the last three, made when the leukocytes averaged 9,286, was one minute, thirty-five seconds.

Differential counts were made in only four cases. Blood containing 14 per cent. of mononuclear cells clotted in two minutes, that with 35 per cent. in two minutes and a quarter, that with 37 per cent. in two minutes and a half, and blood with 39 per cent. in three minutes and three-quarters. I would not generalize from these figures that the greater the number of leukocytes as a whole, and of mononuclear cells in particular, the longer is the coagulation-time, but incline rather to the opinion that they bear no relationship to one another.

6. Bleeding-Time.—Duke determines the bleeding-time by blotting up on absorbent paper at half-minute intervals the blood from a small cut in the lobe of the ear, the rate of decrease in the size of the series of blots—each of which represents one-half minute's outflow of blood—showing the rate of decrease of the hemorrhage. The total duration of such a hemorrhage is called the bleeding-time. Duke states that the bleeding-time is independent of the coagulation-time.

III. NORMAL CONDITIONS AFFECTING THE BODY AS A WHOLE

1. Age.—Hartman believes that the influence of age on the clotting-time is imaginary. He investigated the blood of women and girls of all ages, 16 to 74 years, and always found the clotting-time four minutes and a half, with occasionally four and five minutes, but never observed a dependence of the clotting-time on age in the diseases he investigated. The age of the individual seems to Rudolf also to make little or no difference in the time of coagulation. At 20 C. the average time of children under 12 examined was 8.04 minutes, and of adults 7.72 minutes.

Weiss, using Wright's tubes, observed that the blood in fifty-four healthy adults coagulated in between two and one-quarter minutes and two and three-quarters minutes. Of fifty-eight healthy new-born infants the blood clotted in from two and a half to three and a half minutes in those breast-fed, and in from one and a half to two and a half minutes in those fed artificially.

2. Sex.—According to Rudolf sex has no evident effect, the average time of females he examined being 7.54 minutes and of males 7.76 minutes.

3. Time of Day.—A number of observers have noted a diurnal variation in the clotting-time. Vierordt made five observations on himself over a period of fifty-six days, obtaining a different average clotting-time for each time of day, the longest being between 1:15 p. m., the shortest between 7 and 8 p. m. Hinman and Sladen took independent observations on themselves every hour, working apart and using different coagulometers. The longest time for both occurred at about 9 a. m., the fall from this being gradual until the shortest time during the day was reached at 4 p. m. After this the course for both was the same—a gradual rise. Bürker for three days tested his blood every two hours from 6 a. m. to 10 p. m., arriving at the conclusion that the coagulation-time is longest in the morning and usually diminishes until 2 p. m., after which it usually rises again.

Hartman's last 270 estimations seemed at first to bear out Bürker's hypothesis that a shortening of the clotting-time exists in the early afternoon hours. Most of the tests made in the late morning and especially in the early afternoon, however, were found to be on women after opera-

tion, which explained the shortening of the clotting-time. Further examination of the last 100 tests disclosed that all the cases of shortening of the clotting-time occurred after operation, while women not operated on between 1 and 4 p. m. did not experience this shortening of coagulation. Hartman therefore concludes that in his material a physiological daily fluctuation was not observed.

Addis noticed that the more temperature variation was excluded, the smaller was the amount of difference in the clotting-times, and that fluctuations in the coagulation curves which he formerly had considered as indicative of intrinsic changes in coagulability, were really due to variations in the surrounding temperature. When the temperature variations were entirely excluded, the coagulation-time was found to be remarkably constant at all times of day and night. Slight variations which occur are irregular and due, he believes, to experimental error. For twenty days Addis took the coagulation-time of his own blood and that of certain other persons every hour or two, and in no one of the chart's prepared from these observations do any variations occur which are outside the limit of experimental error.

Rudolf made about 500 estimations of the clotting-time, the results under the same circumstances being constant, but encountered no definite variations at different times of the day. He refers to the fact that, generally speaking, a room will probably be colder in the morning than it will be later in the day, and believes that in any conclusions drawn from experiments in which the temperature of the tubes has not been accurately maintained at the same level, the conclusion would tend to be that the coagulation-time was slower in the morning.

4. Food.—Vierordt refers to an acceleration of blood-coagulation in the hungry. Coleman observed that the longest coagulation-time occurs one hour after the principal meal of the day, the blood becoming less coagulable as absorption becomes established after a meal. Conversely, the shortest time was recorded when the subject was fasting before breakfast. A slight slowing of coagulation about two hours after a meal was noted by Rudolf.

The above accords with my own experience. Of my normal subjects six that were examined with my method before meal-time gave an average clotting-time of seven and one-sixth minutes, while seventeen examined after a meal gave an average time of nine minutes. This would seem to indicate the possibility at least that the coagulation-time is longer after a meal than before it.

Wright, on the contrary, states that restriction of food diminishes coagulability and therefore advocates the abandoning of starvation in cases of aneurysm unless the coagulometer shows improvement.

Mercier in a large number of observations found the clotting-time shortly after a meal constantly less than shortly before a meal.

Addis estimated the clotting-time on ten different occasions both before and after breakfast, obtaining an average time before food of seven minutes, forty-seven seconds, and an average time after food of seven minutes, forty-six seconds. Hartman also proved by tests before and after full meals that the taking of food does not produce variations of the clotting-time.

5. Fluids.—According to Wright, restriction of fluid increases coagulability and *vice versa*.

6. Exercise.—Coleman has demonstrated that there is a certain amount of shortening of the coagulation-time after fifteen or twenty minutes' severe physical exertion. He mentions the possibility of the specific gravity of the blood being slightly increased after loss of fluid from the plasma of perspiration, but as this was not very great during the experiment, he thinks it probable that the slight increase in coagulability was independent of any alteration of the specific gravity.

7. Menstruation.—A number of circumstances point to a possible connection between menstruation and the clotting-time: the occurrence of vicarious menstruation in the form of nosebleed, etc.; the frequent occurrence of hemoptysis at the menstrual period in tuberculous women; and the fact pointed out by Birnbaum and Osten, that menstruating women in many cases bleed remarkably easily and continually at operation, even when the latter is outside of the genital tract, so that some surgeons are unwilling to operate during menstruation. These authors believe that in some way checking of the normal blood-clotting process must accompany the physiological occurrence of menstruation. They found the clotting-time on the average more or less retarded during menstruation. Bode also found retarded coagulation in many menstruating women, though he found it hastened in several cases.

Bell and Hick observed that a very marked drop in the calcium content of the systemic blood always occurs before the menstrual bleeding commences. Often this drop is preceded by a marked rise. Pölzl noted a periodical connection between menstruation and the number of red blood-cells in sexually mature women, the highest count usually being one day before the beginning of the bleeding, from which a quick fall follows, which in no way depends on the blood loss.

Cristea and Denk, on the other hand, found the clotting-time of the systemic blood of menstruating women neither shorter nor longer than normal. They also found a normal calcium content in the blood of menstruating women.

Schwab found a normal average clotting of the blood during menstruation. Hartman will only say that with the method he employs he could never find variations from the normal clotting-time.

With my method I tested the coagulation-time in sixteen tuberculous women who were spitting blood. Four, who were menstruating, had an average clotting-time of five and three-quarter minutes. In two cases of amenorrhea at the menstrual period the average clotting-time was also five and three-quarter minutes. The time was five and two-third minutes in ten who were not at the menstrual period, some having passed the menopause. These few cases consequently do not point to any alteration in coagulability at the catamenia.

Hartman regards the uniform clotting-time in women and girls of all ages as settling negatively the question whether an influence is exerted by the circumstance that a woman is at the menstrual age, or has not entered it, or has passed it.

8. Pregnancy.—Pregnancy probably does not influence the clotting-time. Douglas obtained clotting-times of seven and three-quarter minutes in healthy non-pregnant women and seven and four-tenths minutes in healthy pregnant women. Hartman was not able to determine a deviation from the normal clotting-time during pregnancy, either in the early or in the latter months. Fox made a few observations on women during the latter part of pregnancy which, so far as they go, indicate a tendency to a low coagulation-time, in several cases lower than after delivery.

An increased fibrin content has been noticed by Nasse in the blood of pregnant women.

9. Puerperium.—Douglas obtained an average clotting-time of seven and three-tenth minutes in normal puerperal women, compared to seven and three-quarters minutes in healthy non-pregnant women. Hingston Fox examined eight puerperal women, all primiparas with normal labors and normal hemorrhage, all suckling their infants. He found the clotting-time immediately after delivery to be below the normal.

(To be continued)

ERRATA IN PAPER OF DRS. CHRISTIAN, SMITH AND WALKER

Several errors occurred in the references to illustrations in the paper on "Experimental Cardiorenal Disease," by Drs. Christian, Smith and Walker, last month, pages 468-551. They are as follows:

On page 517, line 41, "Fig. 3" should read "Fig. 14."
On page 518, line 16, "Fig. 7" should read "Fig. 12."
On page 518, line 26, "Fig. 4" should read "Fig. 15."
On page 519, line 12, "Fig. 2" should read "Fig. 13."
On page 521, line 9, "Fig. 1" should read "Fig. 12."
On page 522, line 22, "Fig. 1" should read "Fig. 12."
On page 522, lines 24 and 25, "Fig. 2" should read "Fig. 13," and "Figs. 2 and 3" should read "Figs. 13 and 14."
On page 522, lines 27 and 28, "Fig. 4" should read "Fig. 15."
On page 522, lines 30, 32 and 33, "Figs. 5 and 6" should read "Figs. 16 and 17."
On page 522, line 34, "Fig. 7" should read "Fig. 18."
On page 547, the name in the footnote should be "Mr. L. S. Brown" instead of "Mr. L. L. Brown."

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AN EXPERIMENTAL STUDY OF THE PAIN SENSE IN THE PLEURAL MEMBRANES *

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ANATOMY

The *parietal* pleura receives its innervation from the intercostal, sympathetic and vagus nerves (Luschka,[1] Poirier and Charpy[2]). Following the teachings of Luschka most anatomists state that fibers from the phrenic nerve also enter this portion of the pleura, but the evidence for such belief is not final. Stöhr[3] states that the nerves end partly in the lamellated capsules of Pacini, partly in the smaller corpuscles of Golgi, both of which are endowed with sensory functions.

The *visceral* pleura is supplied by nerve fibers from the pulmonary plexuses which originate in the vagus and sympathetic nerves.

The *pericardial* pleura receives two delicate branches of the vagus coming from the plexus pulmonalis or plexus esophageus, one extending over the anterior, and one over the posterior portion of the sac (Spalteholtz[4]). Most authors state that the phrenic nerve also supplies the pericardium (Van Gehuchten,[5] Ramström,[6] Rauber,[7] Poirier and Charpy).

The Diaphragmatic Pleura.—Luschka (1853) believed that the phrenic nerve gave off sensory nerve fibers to the pleural surface of the diaphragm as well as motor fibers to the muscle. Poirier and Charpy and others (Rauber, Van Gehuchten) confirmed this opinion. Cavalie[8] has demonstrated that the last six intercostal nerves penetrate 1 to 2 cm. into the margin of the diaphragm and supply the muscle; probably they also contribute sensory fibers to the pleural covering.

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* Read at the meeting of the Association of American Physicians at Atlantic City, May, 1911.

1. Luschka: Abstr. in Arch. de méd., Paris, 1854, iv, 284.
2. Poirier and Charpy: Abrégé d'anatomie, Paris, 1908, ii, 983.
3. Stöhr: Lehrbuch der Histologie, Jena, 1906, p. 283.
4. Spalteholtz: Handatlas der Anatomie des Menschen, Ed. 5, B, 1909, iii, 719.
5. Van Gehuchten: Anatomie du Système Nerveux, Ed. 4, Louvain, 1906, p. 425.
6. Ramström: Merkel's and Bonnet's Anat., 1906, BXXX, No. 92.
7. Rauber: Lehrbuch der Anatomie, ed. 7, Leipsic, 1908, p. 314.
8. Cavalie: Jour. de l'anat., Paris, 1898, xxxiv, 199.

Eisler[9] thinks all the intercostal fibers in the diaphragm are sensory.

Gössnitz[10] claims he can trace branches of the sensory intercostal nerves into the diaphragmatic pleura, but can find only short motor branches.

In a most comprehensive study Ramström concludes that the phrenic nerve furnishes sensory branches to the entire pleural and peritoneal covering of the diaphragm except at the rim, where both pleura and peritoneum receive sensory fibers from the sixth to twelfth intercostal nerves. He succeeded in tracing nerve filaments to both the pleural and peritoneal investments of the diaphragm to a point corresponding to the outer third of the distance between the thoracic wall and the central tendon of the diaphragm.

PHYSIOLOGY

Physiologists have contributed very little to our specific knowledge of the sensibility of the pleural membranes, since the investigation cannot be carried on successfully in animals, and these parts are not easily accessible in man. Nevertheless, it is to the physiologic researches of Ross, MacKenzie[11] and, preeminently, of Head[12] that we are indebted for establishing the general laws underlying the production and distribution of visceral pain. The nerves supplying the skin and skeletal muscles have become so educated that any injury to them is accurately located. Such is not the case with the nerves of the internal organs. A painful irritation of the viscera finds expression, not necessarily over the site of the organ, but in a painful area of skin often remote from it. Head has shown that the painful stimulus in the organ travels in a centripetal direction to the posterior part of the cord and there sets up excitation of the nerves which in the same and adjoining segments supply the peripheral surfaces with sensation. The pain is referred to the skin because therein the pain sense reaches its highest development.

"Referred pain" from the viscera has these characteristics to differentiate it from pain of peripheral origin:

1. It is often remote from the site of irritation.
2. It follows lines on the skin of spinal segmentation rather than the course of peripheral nerves.
3. It is usually associated with cutaneous hyperesthesia and tenderness to pressure.
4. Often the pain fails to involve a whole segmental area of the skin, but finds expression in one or more points of maximal tenderness and spontaneous pain.

These generalizations of Head stand to-day unquestioned, but his interpretation of thoracic pains has led him into error. Rightly he states

9. Eisler: Ztschr. f. Morphol. u. Anthrop., 1901, iii, 21.
10. Gössnitz: Beiträge zur Diaphragm, Jena, 1901.
11. Mackenzie: Brit. Med. Jour., 1906, i, 1449.
12. Head: Brain, 1893, 1894, 1896.

that the pain of parietal pleurisy is "local," following the course of the intercostal nerves. But the assertions that referred pains in pleuropneumonia arise from the lungs only; and that serous membranes do not give rise to referred pain, are disproved by clinical experience.

Lenander[13] considers the parietal pleura and pericardium to be highly sensitive to pain as well as the mediastinal tissues. He calls attention to the fact that because of the overlapping of the intercostal nerve-endings within the thorax, every point in the pleura may have fibers from at least two nerves.

CLINICAL

Pain may be elicited in the trachea and bronchial tubes (bronchitis), but there seems to be very little if any pain sensibility in the parenchyma

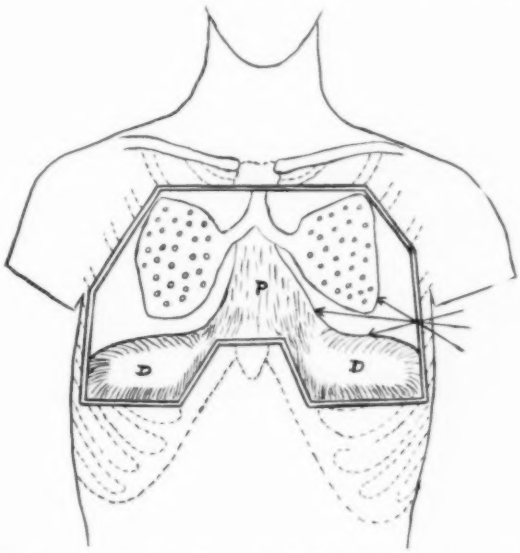

Fig. 1.—Diagram illustrating the method of testing the pleura for sensation. The lungs are retracted by exudate and diaphragm flattened. The arrows represent the wire passing through a hollow trocar and touching, respectively, the pulmonary, pericardial and diaphragmatic pleura.

of the lung. Tumors or simple bronchopneumonia or abscess in the lung may exist without giving rise to pain. The pain in lobar pneumonia is quite generally attributed to the associated pleurisy.

As a rule the pain of pleurisy is situated over the area where the friction sounds are heard — a fact that is readily explained by the intimate relationship of the costal pleura and the intercostal nerves.

13. Lenander: Keen's Surgery, Philadelphia, 1909, v, 1068.

When the pleura over the apex and the upper lobe is involved, pains are common along the upper intercostal nerves, in the supraclavicular and supraspinous spaces and in the brachial plexus. Areas of cutaneous hyperesthesia may be present. Diffuse inflammations of the pleura have a tendency to concentrate the pain in the lower thorax rather than the upper, and in the anterior and axillary portion rather than in the posterior. This is explained by Schmidt[14] by the greater excursion of the chest at the base. Perhaps too the greater sensibility of the skin anteriorly and laterally determines the location of pain and tenderness in these parts. Head has made the interesting observation that if pain is produced in two neighboring areas of the skin at the same time, it may be consciously referred only to that area in which the pain sensibility is most highly developed.

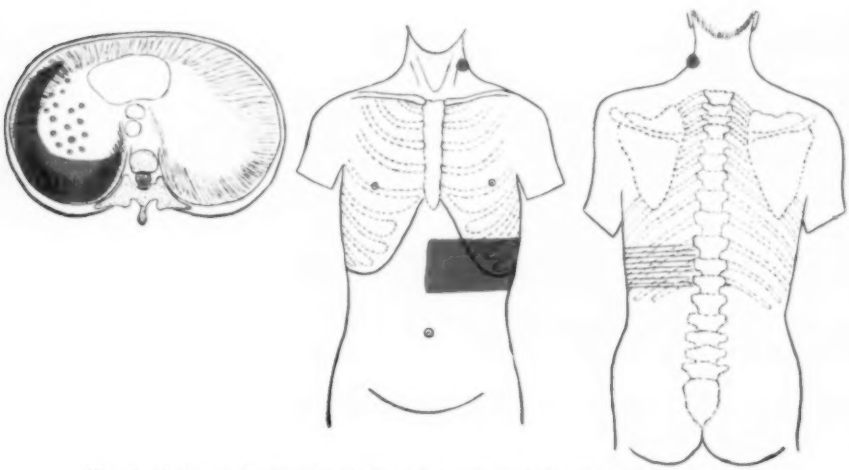

Fig. 2.—Left-sided pleural effusion. Thoracentesis in fifth space, post-axillary line. Typical distribution of pain over lower thorax and epigastrium from pressure on outer margin of diaphragm. Dot in upper trapezius region indicates maximum point of pain elicited by pressure over central part of diaphragm. Solid red: Area giving rise to referred pain in lower thorax and abdomen. Red dots: Area giving rise to referred pain in the neck.

The relative importance of the visceral and parietal layers of the pleura in pain production has not been settled. Pain is often ascribed to inflammation of the visceral pleura, but as the parietal pleura is so often simultaneously involved, the evidence of visceral pleura sensibility is not adequate. The nerve supply to the visceral pleura is exactly the same as that to the alveoli of the lungs (vagus and sympathetic nerves). Knowing as we do that inflammation of the pulmonary alveoli does not

14. Schmidt: Pain. (Transl. by Vogel), London, 1908.

give rise to pain, we must be skeptical of the existence of pain sensibility in the visceral pleura.

Occasionally there is a distinct pleuritic rub without any pain. In such instances, however, pressure over the affected site may elicit tenderness (Musser).[15] "Contralateral pain" or pain referred to the site opposite the lesion is frequently mentioned in the literature. It is possible that such pain is often due to some unrecognized involvement of the pleura or nerves on the side complained of and that this pain is severe enough to obscure the lesser pain over the outspoken lesion.

DIAPHRAGMATIC PLEURISY

Much confusion has prevailed in the clinical description of pain in diaphragmatic pleurisy. As early as 1875 Ferber[16] described a pain

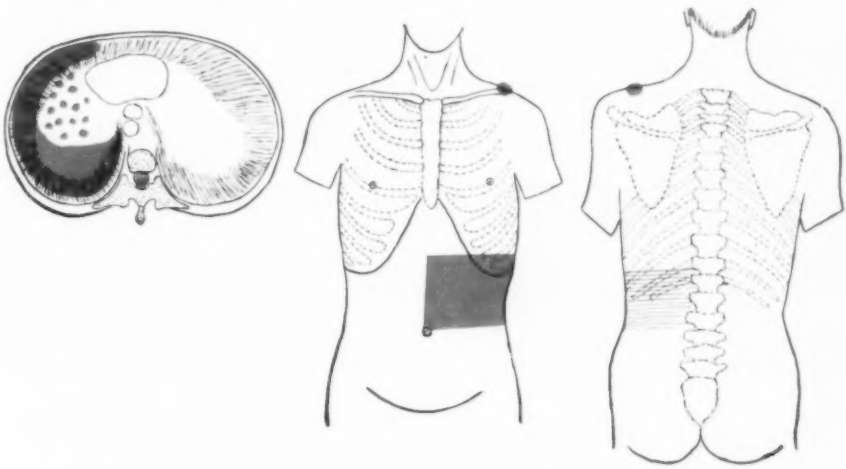

Fig. 3.—Left hydrothorax. Note the extension of pain down to level of navel from irritation of margin of diaphragm. Neck pain referred to lower third of trapezius ridge.

located deep in the thorax from swallowing a morsel of food, occurring in a patient with diaphragmatic pleurisy.

De Mussy[17] (1879) called attention to the prevalence of pain in the lower thorax, often in the epigastrium, and located the maximum tenderness at the intersection of the parasternal line and a horizontal line continuous with the end of the tenth rib (*bouton diaphragmatique*).

Pain in the shoulder region and tenderness over the phrenic nerve in the neck were long ago noted (Andral, De Mussy) and by Luschka

15. Musser: Osler's System Med., Phila., 1907, vol. ii, p. 564.
16. Ferber: Dissert., Marburg, 1875.
17. DeMussy: Arch. gén. de méd., 1879, ii, 5.

attributed to inflammation of the phrenic nerves in the diaphragm. Ziemssen[18] opposed this view of the sensory function of the phrenic nerve. He was unable to excite pain by irritation of the nerve. Schroeder[19] pinched the phrenic nerve below the lower root in a series of eighteen cases during operation for tuberculous glands and in two cases only noted "some pain in the corresponding half of the diaphragm, which subsided before the end of forty-eight hours."

Henocque and Floy (*Comple. rend. Soc. de biol.*, 1882, p. 578) on the other hand observed that "section or ligation of the superior branch of the phrenic nerve was very painful."

All the more recent anatomical and experimental studies confirm Luschka's theory that inflammation of the phrenic nerve endings in the diaphragm are responsible for cervical pain (Toldt,[20] Schreiber,[21] Rauber,

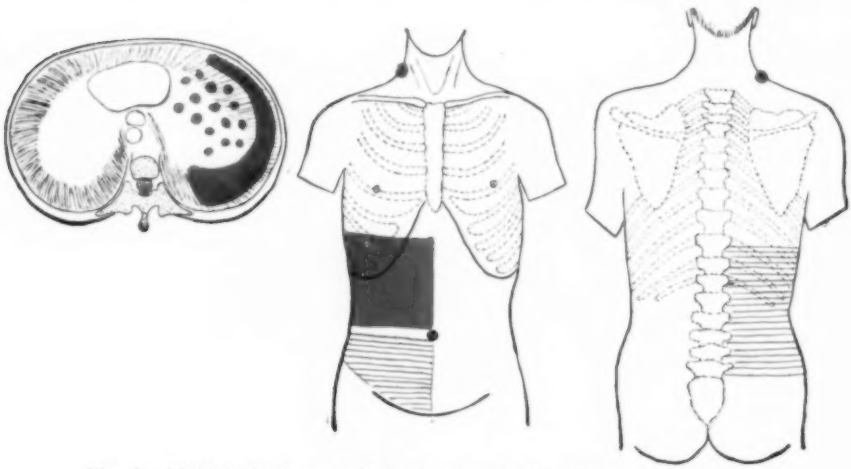

Fig. 4.—Right hydrothorax. Extension of pain downward was proportionate to degree of pressure on diaphragm. With increasing pressure pain spread from upper to lower abdomen.

Stenitzer[22]). Schmidt finds this pain most often located at the junction of the outer and middle thirds of the trapezius muscle. In recent years the frequency of abdominal pain in pleuropneumonia of the lower lobe has been emphasized by Griffith,[23] Herrick[24] and others, and its close simulation of abdominal diseases, e. g., appendicitis and cholecystitis, has

18. Ziemssen: Deutsch. Arch. f. klin. Med., 1882, xxx, 291.
19. Schroeder and Green: Am. Jour. Med. Sc., February, 1902, cxxiii, 29.
20. Toldt: Anatomischer Atlas, Berlin, 1907, p. 820.
21. Schreiber: Arch. f. de ges. Physiol., Bonn, 1883, xxxi, 577.
22. Stenitzer: Wien. klin. Wchnschr., 1903, xvi, No. 16, 465.
23. Griffith: Jour. Am. Med. Assn., 1903, xli, 531.
24. Herrick: Jour. Am. Med. Assn., 1903, xli, 535.

been pointed out. Schmidt states that this pain and tenderness are only brought out by pressure, but the majority of observers definitely speak of spontaneous pain as well. Head attributes the abdominal pain to the involvement of lung tissue rather than of the pleura.

AUTHOR'S CASES

In my series of about 240 cases of pleuropneumonia and pleurisy, careful attention was given, in both the anamnesis and examination, to the distribution of pain. The pain in pleurisy restricted to the upper lobes was usually located in the upper scapular and shoulder region; sometimes in the subclavicular region or supraclavicular spaces; never was the pain felt in the lower thorax or abdomen. In wide-spread pleurisy or in pleurisy over the lower lobes, with or without pneumonia,

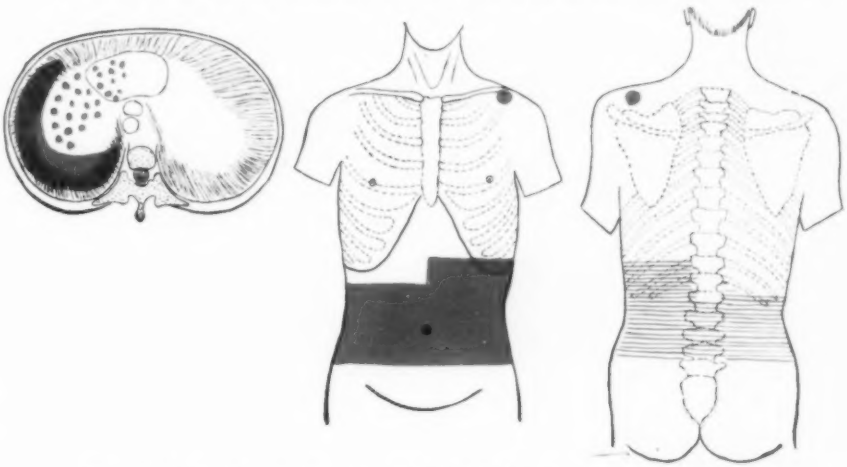

Fig. 5.—Left pleural effusion. Bilateral referred pain from pressure on periphery of diaphragm. Neck pain referred to same point from both pericardium and central diaphragm.

the pain was commonly confined to the lower thorax, especially over the lateral and anterior aspect. *Referred pains*, or pain in parts distant from the site of inflammation, were present in these basal pleurisies with surprising frequency. Nineteen patients altogether complained of pain in the abdomen. Of this number eight experienced pain only in the upper abdomen as far down as the navel (ninth and tenth segments), while eleven had pain over the whole half of the abdomen including the eleventh and twelfth segments. This pain was both spontaneous and induced by pressure. Cutaneous hyperesthesia or hyperalgesia were constant. In eleven of these cases of basal pleurisy, in which an apical involvement could be excluded, pain was referred to the neck region. All but two of

this group were subject also to the abdominal pain, thus suggesting that these widely separated areas are rendered sensitive by irritation of a common structure, viz., the diaphragmatic pleura. Both cervical and abdominal pain might be present for only one or two days and then disappear.

Two of these cases, both exhibiting abdominal pain, and one pain in the neck, came to autopsy. Both showed fibrinous adhesions between the diaphragm and lower lobe.

The maximum points of pain and tenderness in the neck were generally along the trapezius ridge, five times over the central third, twice over the inner and once over the outer thirds, once over the junction of the middle and outer thirds, once below the mastoid process, once over the upper third of the sternomastoid muscle. The pain was in the skin

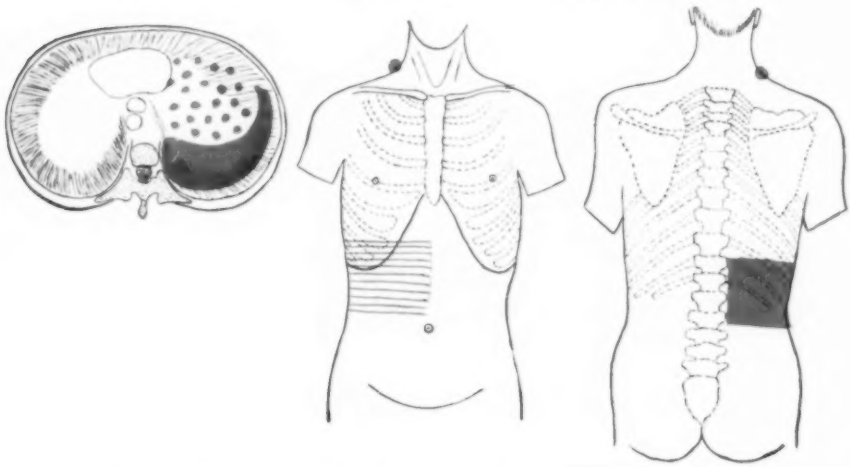

Fig. 6.—Right pleural effusion. Back pain very severe from pressure in crural region.

and superficial tissues and always associated with hyperalgesia. The areas above named are supplied by the cutaneous branches from the fourth cervical segment, with the exception of the last two which are supplied by the third cervical segment.

Although the referred neck pain occurred nearly always in a patient who had also abdominal pain, the two types of pain were not necessarily simultaneous. Often the neck pain came on suddenly during the course of abdominal pain and thereafter took its place, or at least overshadowed it.

Both the cervical and abdominal pain were aggravated by deep inspiration, cough and hiccough. Strapping the chest increased the pain by augmenting the excursion of the diaphragm. Conversely, strapping the abdomen diminished the pain.

The abdominal pain is in the wall only and therefore more superficial than that due to inflammation of the abdominal viscera. I have confirmed Herrick's observation that deep pressure is well borne, provided it is made gently with the flat surface of the hand.

Tenderness over de Mussy's point was noted but twice.

Tenderness over the phrenic nerve I was able to demonstrate in but one instance.

In one case of subphrenic abscess on the left side, following rupture of an ulcer of the stomach, there was pain along the costal border and epigastrium and severe pain in the neck, localized over the middle third of the trapezius ridge.

A patient with leukemia with perisplenitis also complained of a sharp pain in the outer portion of the trapezius region, as well as pain in the

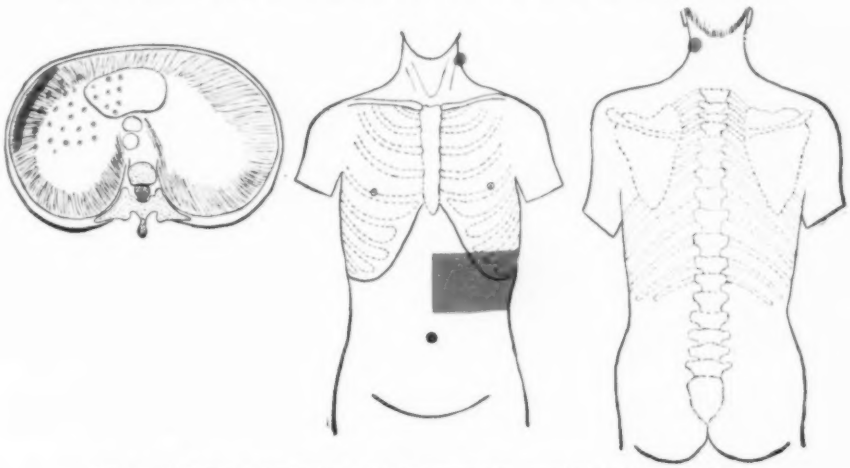

Fig. 7.—Left pleural effusion. Note narrow rim supplied by intercostal nerves. The maximum point of referred pain from median diaphragm and pericardial pleura was identical, i. e., in the submastoid region.

hypochondrium. In both instances the pain was increased by deep inspiration and associated with hyperesthesia of the skin in the same areas.

These cases in which the under surface of the diaphragm was inflamed gave rise to referred pain identical with those observed in affections of the pleural surface of the diaphragm. Hence clinical evidence supports the view of Ramström that the phrenic nerve and the lower intercostal nerves furnish sensory fibers to the peritoneal covering of the diaphragm as well as to the pleural.

EXPERIMENTS

Over two years ago, while clearing out an obstructed cannula inserted low in the thorax for drainage of an effusion, I accidentally pressed with

the stylet on the outer margin of the diaphragm, whereupon the patient complained of pain in the lower thoracic region and upper abdomen. When the stylet was brought into contact with a higher and more mesial portion of the diaphragm, the costal and abdominal pains were replaced by a sharp pain in the neck. Since then I have attempted in every case of thoracentesis available, to explore the pleural surfaces with a long wire and to record the location of the pain so induced.

From a total of over seventy-five thoracentesis operations, only thirty-five have presented conditions favorable to free exploration. In a normal chest the lung fills the cavity and prevents any testing. Likewise firm adhesions block the movement of the wire. In a large effusion of pleuritic origin, or preferably in a pure hydrothorax, the lung is retracted as a rule and the convex diaphragm is flattened out, allowing the wire free

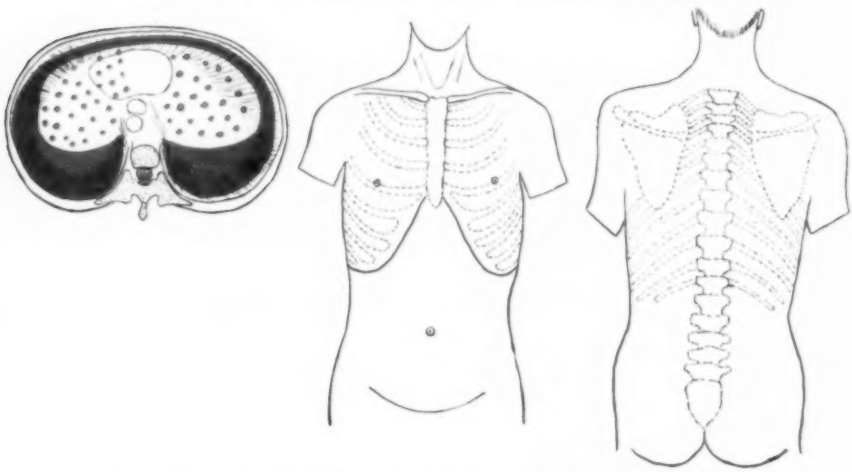

Fig. 8.—Composite diagram showing the sensory supply of diaphragmatic pleura (thirty-five cases). The margin in solid red supplied by intercostal nerves; the dotted area by the phrenic.

play. It is apparent that a pleura covered with a thick exudate may give no response whatever to irritation. On this account positive responses are of more weight than negative. Only when a given portion of the pleura fails to respond constantly in a large number of individuals, can one assume that it is not endowed with pain sensibility.

METHOD

A good-sized trocar is inserted in the thorax and the point withdrawn. Before much fluid escapes, a long stiff wire with a dull point is passed through the cannula and the cavity therewith explored. The lung is easy to distinguish by its spongy resistance. The parietal pleura

can be reached at one or more points distant from the cannula, where the wire point becomes visible, pressing out an interspace. The diaphragm is recognized by its firm resistance and its excursion with respiration, the wire moving in and out like a piston. The pericardium imparts a more rapid impulse that is synchronous with the heart-beats.

VISCERAL PLEURA

The visceral or pulmonary pleura was successfully explored in over fifty cases, in thirty-five of which conditions were favorable. This structure seems devoid of pain sense. Occasionally inward pressure would elicit pain, but this occurred only when adhesions were present and then could be explained by the inward pull of adhesions on the parietal pleura. Other forms of irritation than pressure were tried without inducing any feeling of discomfort.

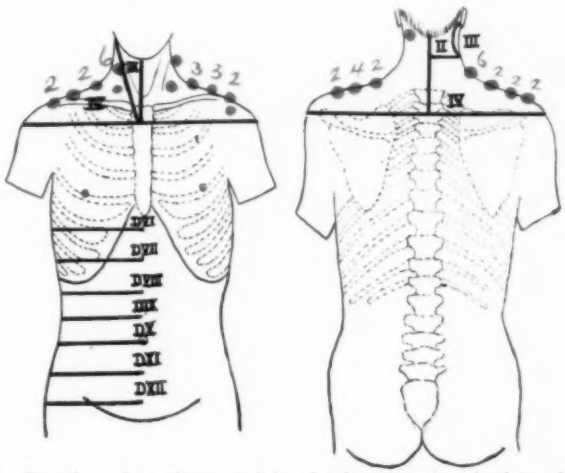

Fig. 9.—Location of maximum points of referred neck pain from diaphragm irritation in twenty-three cases. They all are situated in the regions supplied by the third and fourth spinal segments.

PARIETAL PLEURA

Pressure on the parietal pleura invariably gave rise to sharp pain that was located with remarkable accuracy over the site of irritation. The determination was more exact in the anterior and axillary regions than in the posterior wall. Occasionally the pain was complained of in the intercostal space just below the site of irritation, but the pain exhibited no tendency to spread downward to the costal border or abdomen even with strong pressure of the wire.

DIAPHRAGMATIC PLEURA

An area of the diaphragm including the crural region, and corresponding roughly to the posterior third, was tested more or less extensively in

thirty cases. Pain was almost constantly elicited and localized in the lower, posterior thorax of the side irritated. This pain was dull, yet frequently severe and often spread over the lumbar muscles and flank. In seven instances the pain extended to the lateral and anterior aspects of thorax and abdomen. Once the pain was referred over the abdomen on both sides as well as over both sides of the back. The pain was not sharply defined, but diffuse.

The portion of the diaphragm immediately attached to the chest wall could not be reached by the wire. Perhaps a margin of one or two inches was thus unexplored in all cases, while in certain instances, especially when the cannula entered the posterior part of the chest, a somewhat broader margin was beyond reach. Irritation of the peripheral zone in twenty-six cases excited pain in the lower thorax, laterally and anteriorly, especially along the costal border. In a large proportion of experiments

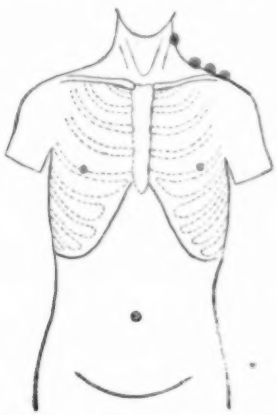

Fig. 10.—Location of points of maximum pain from irritation of pericardial pleura in five cases. All lie in fourth spinal segment.

the pain passed beyond the costal edge to the epigastrium. The degree of irritation had a decided influence on the intensity and the spreading of the pain. Strong pressure on the wire often resulted in an extension of the pain from the lower thorax and epigastrium to the lower abdomen.

As the wire was moved from the outer border of the diaphragm toward the center, the pain as a rule suddenly changed and was referred to the neck. In most of the negative cases there was either difficulty in reaching this part of the diaphragm or evidence of exudate. Working back from center to periphery, the neck pain abruptly ceased and the low thoracic pain reappeared. I endeavored to measure the width of the rim, from the marginal attachment responding by thoracic pain, to the point at which the neck pain begins. The estimated width varied from 1 to 4 inches in

different individuals, the average being between 2 and 3 inches. This margin was much narrower anteriorly and laterally than posteriorly, where the band so enlarged as to include the posterior third of the diaphragm. In this marginal zone irritation caused pain in the lower thoracic and abdominal regions (see diagrams).

NECK PAIN

The central or median surface of the diaphragm (the posterior third segment excepted) gave rise to pain in the neck in twenty-three of thirty-five cases. The cervical pain was sharp, lancinating and referred with astonishing frequency to certain areas overlying the trapezius muscle ridge. Seven times the pain was located over the inner third of the trapezius; five times over the middle third; four times over the outer third; four times at the junction of outer and middle thirds; two times over the supraclavicular fossa; once over the coracoid process.

The pain was situated in the skin and superficial structures, was characterized by a point of maximum intensity, and was associated with cutaneous hyperalgesia over the surrounding area. The maximum pain-point in a given individual was the same, from whatever part it was elicited. If, for example, irritation of the anterior part of the dome of the diaphragm excited pain over the inner trapezius region, then the location of all pain referred to the neck from irritation of neighboring points on the diaphragm was at exactly the same place. In other words, the maximum point for referred pain in the neck is peculiar to the individual and constant.

PERICARDIAL PLEURA

The pericardium is more difficult to test than any other pleural membrane, because it is deeply situated and is often covered by a thin layer of collapsed lung. As a consequence negative results are not conclusive.

In nine experiments in which the wire seemed to be in direct contact with the pericardium and transmitted every heart impulse, four yielded no evidence of sensibility. In the remaining five the test gave rise to pain in the neck of the same character as that produced by irritation of the central diaphragm. The pain was the same from pressure over both upper and lower portions of the pericardium. Twice the maximum pain was referred to the outer third of the trapezius ridge, once to the junction of middle and outer thirds, once to the middle third and once to the inner third of the trapezius ridge.

It is remarkable that the maximum point of neck pain in a given person was *identical* whether the pericardium or median portion of the diaphragm was irritated. Thus we have strong evidence that the pericardial and central diaphragmatic pleura have the same nerve-supply.

COURSE OF PAIN IMPULSES

After these clinical and experimental observations, we are in a position to trace the course of sensory impulses arising in the pleura.

The pain evoked from the parietal pleura has all the characteristics of peripheral nerve pain, viz., the pain is located directly over the site of irritation; there is tenderness to deep pressure over the intercostal nerves; the skin, as a rule, is not hypersensitive. The important diagnostic point is that in no instance was a simple parietal pleura irritation accompanied by pain in the abdomen. We may conceive that in parietal pleurisy the intercostal nerve-endings in the pleura are directly irritated or inflamed and the picture is that of neuralgia or neuritis in a peripheral nerve. Pain in the shoulder or arm may be explained by a direct implication of the upper intercostal nerves and brachial plexus.

The pain proceeding from the pleura of the diaphragm is of an entirely different type. The lateral and anterior margins and the posterior third of the diaphragm give rise to pain, not in the diaphragm itself, but in a diffuse area over the lower thorax, back and abdomen. This is true "referred pain," since it is segmental in its distribution; it is located in the peripheral tissues, more especially in the skin; it is accompanied by cutaneous hyperesthesia and tenderness and often by muscular rigidity. To explain the production of this pain, we assume that afferent sensory impulses originating in the nerve-endings of the diaphragmatic pleura (sixth to twelfth intercostal nerves), travel to the posterior part of the spinal cord and there excite pain in the corresponding spinal cutaneous segments (Head).

The neck pain from the inner surface of the diaphragm is likewise a typical "referred" pain. The areas of pain localization described both clinically and experimentally were, for the most part, in the distribution of the fourth cervical cutaneous segment (trapezius ridge and acromial region); occasionally in the third cervical cutaneous segment (submaxillary and submastoid regions). There is every reason to suppose that the afferent impulses from the diaphragm are carried up the phrenic nerve to the cervical cord where painful stimuli are set up in the corresponding cutaneous segment. As anatomists find that the phrenic is chiefly made up of fibers from the fourth cervical nerve, we can understand the greater frequency of pain in the fourth cutaneous segment. It is possible that in those cases characterized by referred pain in the third cutaneous segment, the phrenic nerve is more largely derived from the third cervical nerve.

The pain induced by irritation of the *pericardial pleura* was always (five times) situated in the fourth cutaneous cervical segment and was of exactly the same character as the neck pain of diaphragmatic origin. The well-known distribution of phrenic nerve fibers to the pericardium

strengthens the conviction that afferent impulses follow up the phrenic nerve to the cord and there stimulate painful sensation in the corresponding cutaneous segment. Furthermore, the identity of the nerve-path from diaphragm and pericardium is shown by the fact that from both structures in the same individual the maximum region of neck pain is precisely the same.

Why in a certain individual the referred neck pain is always limited to a restricted area or spot and not located over the whole cutaneous segment, is a subject for conjecture. Perhaps a close anatomic relationship exists between the phrenic and a certain group of fibers in the segment—this relationship being peculiar to the individual.

SENSORY DISTRIBUTION OF PHRENIC NERVE

By means of these experiments we are enabled to trace quite definitely the sensory distribution of the phrenic nerve to the pleura.

The phrenic nerve supplies the anterior two-thirds of the diaphragmatic pleura, with the exception of a peripheral band of varying width. The nerve fibers spread out from the central nerve trunk toward the border, where they come in contact with the sensory fibers of the last six intercostal nerves. Although the transition from phrenic to intercostal pain is usually abrupt, still there is evidence that the fibers interlace. Occasionally along the zone of contact moderate pressure produced pain of intercostal type while stronger pressure set up pain of phrenic origin in the neck.

The phrenic nerve seems to be the chief if not the only sensory supply of the pericardial pleura. Experimental and clinical data afford no evidence of a sensory innervation of the parietal pleura by the phrenic nerve.

SENSORY DISTRIBUTION OF INTERCOSTAL NERVES TO THE PLEURA

That the intercostal nerves give off sensory fibers to the diaphragmatic pleura as well as motor fibers to the muscles has been long surmised without being proved. But these experiments give us for the first time definite physiological proof of the existence of these sensory fibers and an idea of the extent of pleura thus supplied.

The last six intercostal nerves send their sensory fibers into the diaphragmatic pleura at the costal attachment, innervate a peripheral band varying in width anteriorly and laterally from 1 to 4 inches and averaging from 2 to 3 inches. Posteriorly the intercostal sensory fibers penetrate deeply and supply the whole crural region.

The intercostal nerves richly endow the parietal pleura with sensory nerves and it is possible that they alone perform this function.

CONCLUSIONS

1. The *visceral* pleura is not endowed with pain sense.

2. The *parietal* pleura is richly supplied with sensory fibers from the intercostal nerves. Irritation of the pleura induces sharp pain that is *accurately* located by the individual over the spot that is touched. Such irritation never gives rise to "referred pain" in the neck or in the abdomen. The power to locate sensory impressions seems more highly developed in the anterior and lateral aspects than in the posterior.

3. The *diaphragmatic* pleura derives its sensory supply from two sources, the phrenic nerve and the last six intercostal nerves. The *central* portion of the diaphragmatic pleura is innervated by the phrenic nerve. Irritation of this portion sets up pain in the neck. A peripheral rim of the diaphragmatic pleura, which is 2 or 3 inches wide anteriorly and laterally, and a segment corresponding to the posterior third of the membrane, are innervated by the sensory fibers of the intercostal nerves. Irritation of these areas gives rise to pain in the lower thorax, in the lumbar region or in the abdomen.

The *neck pain* arising from irritation of the central portion of the diaphragmatic pleura is a true referred pain, the afferent impulses reaching the cervical cord through the phrenic nerve trunk and exciting efferent impulses in the skin and superficial tissues supplied by the third and fourth spinal segments. This pain is characterized by a point of maximum pain and tenderness and by a surrounding zone of cutaneous hyperesthesia and hyperalgesia. The maximum point of pain has a remarkable tendency to appear along the ridge of the trapezius muscle (fourth spinal segment).

The pain elicited by irritation of the peripheral or posterior portion of the diaphragmatic pleura is also a true "referred pain." The pain is usually distributed in segmental areas over the lower thorax and epigastrium, sometimes extending downward over the whole abdomen on the same side (seventh to twelfth dorsal segments). The pain is both spontaneous and is associated with hyperesthesia and hyperalgesia of the skin and superficial tissues on pressure.

The *distribution* of the pain is determined by the degree of irritation and by the part that is touched. The more intense the irritation of the pleura, the greater the tendency of the pain to spread down over the lower abdomen. Rarely from strong pressure the pain is *bilateral*, extending over both sides of the abdomen. When the posterior portion of the diaphragmatic pleura is irritated the pain is most marked in the lumbar region.

4. The *pericardial pleura* receives its sensory innervation chiefly if not exclusively from the phrenic nerve. Irritation of this part of the pleura is followed by pain in the neck of the same character and in the same

locations as that induced by irritation of the central portion of the diaphragmatic pleura. This pain is a "referred pain," characterized by a maximum point of tenderness and pain, by hyperesthesia and hyperalgesia to pressure of the surrounding skin, and by muscular rigidity.

5. In an extensive series of cases of diaphragmatic pleurisy in some of which the diagnosis was confirmed by autopsy, pain of the segmental type over the lower thorax, abdomen or lumbar region was present in the great majority. In about one-half the cases pain in the neck was complained of. This cervical pain was always in the region supplied by the third and fourth spinal segments, showing a preference for the trapezius ridge. There was always a point of maximum pain and a surrounding area of hyperalgesia and hyperesthesia of the skin.

6. As a result of a few observations it is believed that there is considerable clinical evidence to show that the phrenic and intercostal nerves supply the peritoneal surface of the diaphragm with pain sense as well as the pleural.

THE RELATION OF THE PAPILLARY MUSCLES TO MITRAL REGURGITANT MURMURS*

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The murmur of mitral regurgitation is heard principally in three locations, namely, about the point of maximum impulse, over the upper portions of the chest to the left of the sternum, and over the back of the thorax in the region about the lower angle of the scapula. The discussion started by Naunyn[1] in 1868 regarding the cause of the murmur in the second left intercostal space, and continued by Curschmann,[2] Balfour,[3] Russell,[4] Bramwell,[5] Gibson[6] and Mackenzie[7] has been reviewed by G. A. Gibson.

In the back, explanations of the presence of the murmur have been offered by Duroziez[8] and also, among others, by Hirschfelder.[9]

At the apex, however, where the propagation is opposite to the direction of the regurgitant stream, though there has been much speculation, no serious experimental proof has been adduced to explain the clinical findings. Hirschfelder[9] has suggested that "the vibrations of the mitral valve may be transmitted to the anterior papillary muscle and apex by the papillary muscles, which act like violin strings."

That the papillary muscles are structures of great importance has been shown by a number of workers. Fenwick and Overend[10] believe that functional and organic changes in these muscles constitute a very important factor in the production of anemic cardiac murmurs. Because of their blood-supply — end-arteries — these muscles furthermore are easily vulnerable to fatigue.

Sewall[11] has shown their importance in maintaining sufficiency of the valves. During the rising tension of systole, the edges of the auricular

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*The same relation, of course, applies to the tricuspid regurgitant murmurs.

1. Naunyn: Berl. klin. Wchnschr., 1868, v, 189.
2. Curschmann: Berl. klin. Wchnschr., 1868, v, 189.
3. Balfour: Clinical Lectures on Diseases of the Heart and Aorta, 1898, pp. 170, 218.
4. Russel: Investigations into some Morbid Cardiac Conditions, 1886, p. 56.
5. Bramwell: Diseases of the Heart and Thoracic Aorta, 1884, pp. 203, 442.
6. Gibson: Jour. Path. and Bacteriol., 1896, iii, 32 and 1897, iv, 465.
7. MacKenzie: Jour. Path. and Bacteriol., 1894, ii, 309.
8. Duroziez: Traité clinique des maladies du coeur, 1891, pp. 316, 485.
9. Hirschfelder, A. D.: Diseases of the Heart and Aorta, 1910, 332.
10. Fenwick and Overend: Brit. Med. Jour., 1891, i, 1117.
11. Sewall: Am. Jour. Med. Sc., 1908, cxxxvi, 32.

valves are forced somewhat into the cavity of the auricle. The terminal act of the ventricular systole, however, is marked by a sharp downward jerk of the valves as the wave of the contraction invades the papillary muscles. With failure of these muscles to contract, these bands stretch like elastic cords, and as the ventricular parietes approximate in systole, a leakage through the upward pushed valves is to be expected. They furthermore assert that a reduplication of the first sound at the apex, usually heard in the erect posture, is due, for the most part, to a late contraction of the papillary muscles of the left ventricle, causing a corresponding and isolated sound of valve tension; and that the systolic murmur in the recumbent position is due to a real valvular insufficiency from imperfect papillary contraction.

The statements made by Roy and Adami[12] and by Fenwick and Overend,[10] that the papillary muscles begin to contract after the contraction of the ventricular wall and finish contracting before the ventricle relaxes, have been disputed by Haycraft and Paterson,[13] who conclude from their experimental work that the contraction of the papillary muscles and of the heart-wall occur synchronously.

In an endeavor to determine if the papillary muscles might not have a still further function, as Dr. Hirschfelder suspected, in transmitting the mitral murmur to the apex, we undertook at his suggestion an experimental study of these muscles in the pig's heart.

The experiments were performed on excised pigs' hearts. A cannula was introduced into the aorta in certain of these, in others into a pulmonary vein, in others again directly into the left ventricle through the mitral orifice, and also through the apex. Water entered the chamber, thus, by various routes in the succeeding experiments. As we had to deal with normal hearts, after the closure of the mitral valve no murmur was audible at any point over the heart. Insufficiencies of the mitral valve were produced in different ways as will be explained later, and definite murmurs created which were heard over the heart, varying in intensity according to the location.

In each experiment a preliminary chart of the heart was made, mapping out the distribution of the murmur prior to any alteration in the papillary muscles or the heart-wall. A second chart was drawn in each case after the specific operation of the experiment had been carried out. The observations were based on a comparison of these two sets of charts.

EXPERIMENT 1.—A small cut was made in the edge of the posterior flap of the mitral valve near the heart-wall, thus localizing the lesion close to the septum on the anterior wall of the left ventricle. The current entered through the aorta.

Observations.—The murmur of greatest intensity was heard around the auriculoventricular junction, being louder over the front of the left ventricle

12. Roy and Adami: Practitioner, 1890, xlix, 81.
13. Haycraft and Paterson: Jour. Physiol., 1895-96, xix, 262.

than the back. This gradually diminished in intensity from the base to the apex. The entire front of the heart showed a greater intensity of the murmur than the back, in corresponding locations.

EXPERIMENT 2.—A small slit was made in the posterior flap of the mitral valve close to the heart-wall, at the opposite end from that in the preceding experiment. This localized the lesion on the back of the left ventricle near the septum. The stream entered as in Experiment 1.

Observations.—Again the intensity of the murmur was greatest around the auriculoventricular junction, but here it appeared louder over the back of the left ventricle than over the front. The intensity over the entire back of the left ventricle was greater than that over the front at corresponding distances from the base.

Experiments 1 and 2 show that in lesions in proximity to the anterior wall of the left ventricle and in lesions close to the posterior wall, the murmurs of greatest intensity are found around the auriculoventricular junction. The charts of the following experiments demonstrate that the

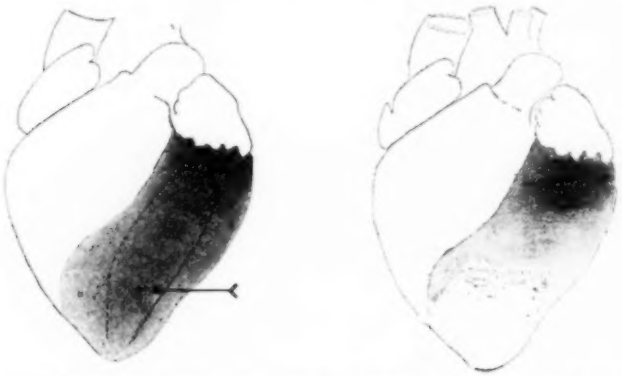


Fig. 1.—Diagram to show distribution of murmur before changes were made in left ventricle. Anterior view. Arrow points toward papillary muscle.

Fig. 2.—Diagram to show distribution of murmur after removal of all of anterior papillary muscle except the portion into which the chordæ tendineæ were inserted. Experiments 3, B, and 5.

murmur is likewise of greatest intensity around the auriculoventricular junction, regardless of the location or nature of the lesion. Furthermore, these experiments make it clear that the intensity of the murmur at any point depends on the distance of the lesion from this area.

EXPERIMENT 3.—A: Artificial vegetations, consisting of knotted string and thread, were attached to the anterior mitral flap in order to produce a murmur. The current entered the aorta. An insufficiency was noted only when these vegetations were relatively very large and decidedly irregular in form. On the other hand, a finger, an artery clamp, a pair of scissors, or a glass rod introduced between the edges of the segments failed to influence the efficiency of the valve.

B: Direction of the current the same as in A. The anterior papillary muscle was completely removed from the ventricular wall, with the exception of a small portion immediately surrounding the insertions of the chordæ tendineæ.

A stitch was taken through one of the flaps, and drawn taut to simulate a sclerosed condition. An insufficiency resulted as soon as the valve segment was slightly drawn up.

Observations.—Over a limited region on the front of the heart where the papillary muscle remained, the murmur appeared relatively louder than before the dissection. On the contrary, there was a great decrease in the intensity of the murmur heard over the areas between this region and the apex. The murmur over the back of the heart, however, remained practically unchanged, except at the apex where it was diminished considerably in intensity.

Conditions leading to a puckering of the valve segments are decidedly more effective in bringing about regurgitations than structures attached to the edges of these segments.

The papillary muscle evidently plays an important rôle in transmitting the murmur of mitral regurgitation toward the apex.

EXPERIMENT 4.—The heart was prepared as in Experiment 3, B, and further altered by removing the lower half of the posterior papillary muscle.

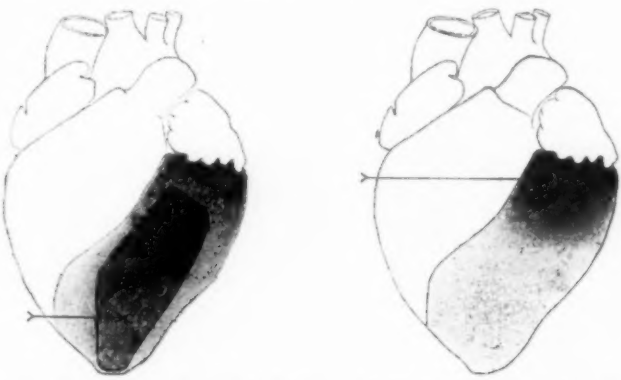


Fig. 3.—Diagram to show distribution of murmur after removal of heart-wall over anterior papillary muscle. Portion removed indicated by outlined area. Experiment 6. Arrow points toward part of wall removed.

Fig. 4.—Diagram to show distribution of murmur after insertion of chordæ tendineæ into heart-wall, as indicated by ring. Experiment 13. Arrow points toward insertion of cords.

Observations.—Over the front of the heart, the murmur showed the same changes as in Experiment 3 B. A similar decrease of the murmur appeared over the lower portions of the back of the left ventricle. The murmur at the apex was relatively much less than in the preceding experiment. Over the upper portions of the posterior aspect, however, the intensity was practically unchanged.

The two papillary muscles apparently share equally the rôle of transmitting the insufficiency murmur to the apex, since the removal of both of the papillary muscles decreases the sounds heard at the apex much more than the removal of only one muscle.

EXPERIMENT 5.—A cut in one of the mitral flaps produced the insufficiency for this experiment. The current entered through the aorta. The anterior papillary muscle was excised as in Experiment 3 B.

Observations.—The findings were identical with those in Experiment 3 B.

These results corroborate the previous conclusions.

EXPERIMENT 6.—A: The direction of the stream and the nature of the insufficiency were the same as before. The ventricular wall immediately overlying the anterior and the posterior papillary muscles was removed to a depth corresponding to the thickness of these muscles.

Observations.—In these areas, both front and back, the murmur appeared greatly increased in intensity.

B: The right ventricular wall was removed to expose the septum. Two areas were chosen of practically the same intensity of murmur. From one of these, the septal wall was removed to a considerable depth.

Observations.—Here, in contrast to A, the murmur was somewhat decreased.

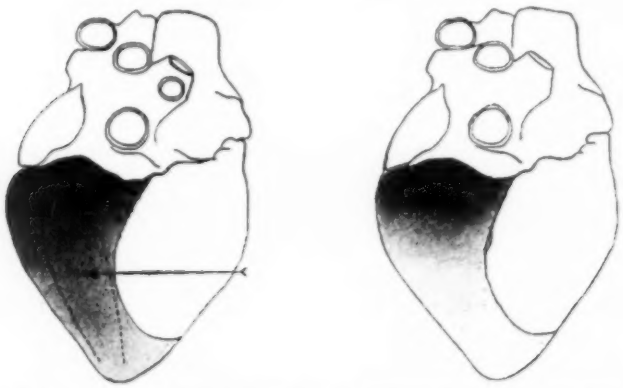


Fig. 5.—Diagram to show distribution of murmur before changes were made in left ventricle. Posterior view. Arrow points toward papillary muscle.

Fig. 6.—Diagram to show distribution of murmur after transplantation of posterior papillary muscle to the septum. Experiment 10.

The transmission of the murmur toward the apex apparently depends only in small part on the thickness of the ventricular wall, as might be inferred from those cases in which the lower portions of the papillary muscles were removed.

C: A section about 1 cm. in width was cut out of the upper portion of each papillary muscle, completely interrupting, in this way, all of the fibers extending toward the apex.

Observations.—A striking diminution in the intensity of the murmur appeared over the areas below these cuts.

The papillary muscles, it seems, must be intact to conduct the murmur.

EXPERIMENT 7.—An artificial stenosis of the mitral valve was produced. The stream, entering through a pulmonary vein, was sufficient in volume to

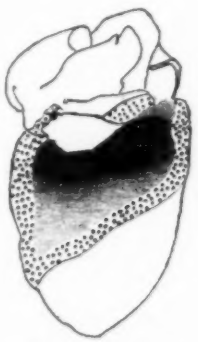
cause a considerable distention of the heart-wall. Portions of the ventricle overlying each papillary muscle were removed as in Experiment 6, A.

Observations.—A very marked increase in the intensity of the murmur was observed over the dissected areas.

Under conditions of high tension within the ventricle, in cases of stenosis, the papillary muscles act as transmitters of murmurs arising in the mitral valve. For further explanation see Experiment 11.

EXPERIMENT 8.—A long tube was inserted into the aorta and partially compressed to simulate peripheral resistance. At the mitral valve, an insufficiency was made. The stream entered through an opening in the apex and flowed out in two directions, namely, the aorta and the mitral valve. These conditions approximated more the currents in mitral regurgitation. The lower three-fourths of the anterior papillary muscle was excised as in previous preparations.

Observations.—As was anticipated, a rumbling sound enveloped the apical areas. The mitral murmur, quite distinct in quality from this, became inaudible over this region. Above these areas, however, overlying the central third of the papillary bed, the murmur appeared definitely diminished.



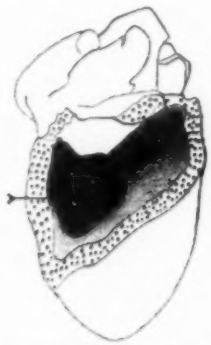


Fig. 7.—Diagram to show distribution of the murmur over the interventricular septum before any changes were made in left ventricle.

Fig. 8.—Diagram to show distribution of murmur after transplantation of posterior papillary muscle to the septum. Experiment 10. Arrow points toward papillary muscle.

As this experiment indicates, the direction of the stream within the ventricle does not appear to alter materially the propagation of the murmur of mitral incompetence.

Since these conditions still varied considerably from those in the pulsating heart, the following experiment was devised:

EXPERIMENT 9.—A: A tube of wide caliber was introduced into the ventricle through the mitral orifice in such a manner as to conduct the stream to the vicinity of the apex. Compression of the aorta provided conditions simulating peripheral resistance.

Observations.—No sound was audible over the ventricular wall. Due to the perfect apposition of the mitral flaps to the cannula, no incompetence occurred at the valve.

B: A cut in one of the valve segments now furnished a regurgitation.

Observations.—Under these conditions, the intensity of the murmur appeared greatest about the auriculoventricular junction. It gradually diminished toward the apex. Comparing the chart of this experiment with the preliminary charts of those experiments in which the stream entered the aorta (3, 4, 5 and 6), the propagation of the murmur over the ventricular wall appeared the same.

C: With the heart the same as in B, Experiment 4 (removal of lower three-fourths of anterior and posterior papillary muscles) was repeated.

Observations.—The intensity of the murmur over the lower areas of the ventricle showed a marked decrease. At the apex it could scarcely be heard, the effect being even more striking than in Experiment 4.

The results of this experiment justify the assumption made in Experiment 8, namely, that the direction of the stream within the ventricle does not alter materially the propagation of the murmur by the papillary muscles.

Since the papillary muscles, *in situ*, play the most important rôle in transmitting the murmur of incompetency to the apex, it is reasonable

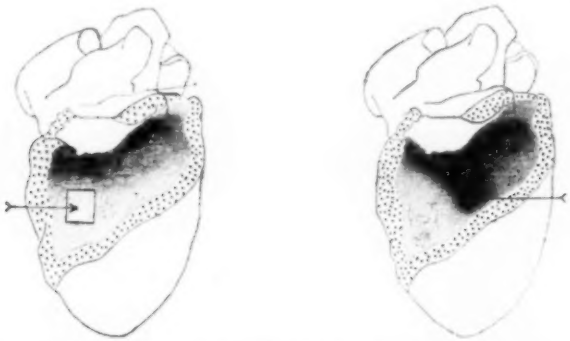


Fig. 9.—Diagram to show distribution of the murmur after removal of part of interventricular septum, as indicated by square. Experiment 6, B. Arrow points toward part of wall removed.

Fig. 10.—Diagram to show distribution of murmur after insertion of chordæ tendineæ into interventricular septum, as indicated by ring. Experiment 6. Arrow points toward insertion of cords.

to conclude that if they were transplanted to other locations the murmur would be conducted chiefly to such regions. To confirm such a conclusion Experiments 10 and 11 were devised.

Experiment 10.—The posterior papillary muscle, in its entirety, was removed from its attachment to the wall of the left ventricle. To expose the interventricular septum, the right ventricular wall was cut away. The papillary muscle was now closely attached to the septum. Again a cut in the mitral valve provided the necessary insufficiency. The current entered through the aorta.

Observations.—A slight diminution in the intensity of the murmur was noted over the lower portions of the front of the left ventricle. Over the areas from which the posterior papillary muscle had been removed, however, the intensity of the murmur was markedly decreased. At the apex the murmur was exceedingly faint. On the other hand, over the region on the septum to which the

papillary muscle was attached, there was a great increase over the murmur previously heard.

EXPERIMENT 11.—The anterior papillary muscle was fastened to the septum and the right ventricular wall removed as in the preceding experiment. A stenosis made at the mitral valve permitted the introduction of the current through a pulmonary vein, i. e., into the auricle.

Observations.—The murmur over the front of the ventricle, especially over the lower half and apex, appeared definitely decreased in intensity. Again, on the septum over the area of attachment of the papillary muscle, the murmur showed a much greater intensity than previously.

These experiments make it clear that the papillary muscles conduct murmurs arising at the mitral valve to whatever portions of the heart they are attached.

In the latter experiment, the high tension maintained in the left ventricle undoubtedly kept the chordæ tendineæ and the papillary muscles

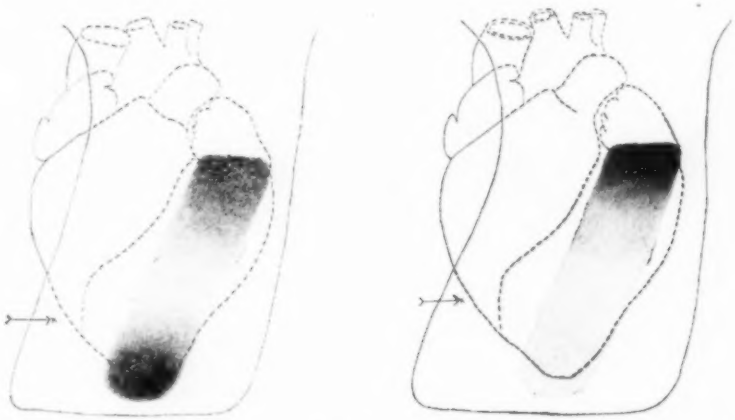


Fig. 11.—Diagram to show distribution of murmur over the lung when the latter was superimposed on the heart. Experiment 15. Arrow points toward lung.

Fig. 12.—Diagram to show distribution of the murmur over the lung after removal of all of the papillary muscles except the portions into which the chordæ tendineæ were inserted. Experiment 15. Arrow points toward lung.

taut, thus furnishing the suitable conditions in these structures for transmission of murmurs toward the apex. Although very unlike the conditions found *intra vitam* in mitral stenosis, the results of this experiment, nevertheless, demonstrate that the chordæ tendineæ conduct the sounds produced by the valve segments to the papillary muscles, and that the latter in turn conduct them to the apex.

The findings in the previous experiments led to the further speculation that, since each papillary muscle conducts the murmur to the heart-wall, if superimposed, one on the other, the intensity of the murmur

should be increased over the latter area. Accordingly, these conditions were produced in the following preparation:

EXPERIMENT 12.—The anterior papillary muscle was removed as in Experiment 11, and attached to the medial surface of the posterior papillary muscle. The current entered at the aorta and flowed out through a lesion in the mitral valve.

Observations.—The area over the front of the left ventricle, from which the anterior papillary muscle had been removed, showed a marked diminution of the murmur. Over the posterior papillary muscle, however, the intensity of the murmur appeared exceedingly increased.

These observations further confirm the conclusions drawn from the preceding experiments.

The work of J. B. MacCallum[14] has shown that there are several layers of muscles entering into the formation of the heart. Nearly all begin in the auriculoventricular ring of one ventricle and end in the

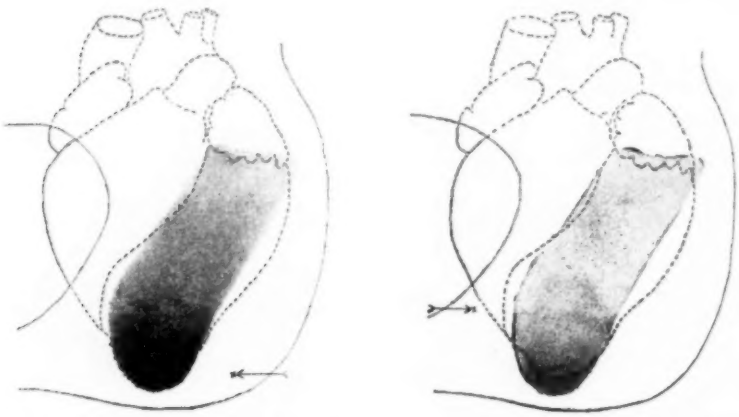


Fig. 13.—Diagram to show distribution of the murmur over the lung when the latter was superimposed on the heart. Experiment 17. Arrow points toward lung.

Fig. 14.—Diagram to show distribution of murmur over the lung after transplantation of the anterior papillary muscle to the interventricular septum. Experiment 17. Arrow points toward lung.

papillary muscles of the other. Those fibers which begin near the outside of one ventricle end near the inside of the other ventricle. The fibers, then, have either a spiral course in the ventricular wall, or else run nearly at right angles to the long axis of the organ, forming the scroll which MacCallum describes.

In the papillary muscles, however, the direction of the fibers is approximately vertical, running from apex to base. In spite of this well-

14. MacCallum, J. B.: Contributions to the Science of Medicine, Welch, 1900, 307.

known fact, no experiments, so far as can be ascertained, have been carried out to determine whether the direction of the muscle-fibers influences the propagation of murmurs toward the apex. If the vertical arrangement of the fibers in the papillary muscles does offer a more suitable condition for the transmission than the spiral course of the fibers in the wall, then the intensity of the murmur over the apical areas should be diminished by connecting the parietal fibers with the chordæ tendineæ.

EXPERIMENT 13.—The chordæ tendineæ were detached from each papillary muscle and inserted into the ventricular wall directly above the corresponding papillary muscle, the latter structure being left intact. The current entered at the aorta. A cut in one of the valve segments furnished an insufficiency.

Observations.—The murmur heard over the lower portions of the ventricle, front, back and apex, was definitely diminished in intensity. But over the areas of attachment of the cords the sounds heard were distinctly louder than before the change.

The vertical direction of the fibers in the papillary muscles does account then, in great part, for the conduction of the murmur along these structures.

EXPERIMENT 14.—In this experiment the cords of the anterior papillary muscle were removed and fastened to the interventricular septum. The right ventricular wall was removed. The current entered through the aorta. A lesion in one of the mitral flaps again provided the necessary regurgitation.

Observations.—A definite decrease in the murmur appeared over the lower front and apex of the ventricle. Over the point of attachment of the cords, on the other hand, a marked increase could be noted.

There can be no doubt, from a consideration of these observations, that the chordæ tendineæ transmit the murmur from the mitral valve to the structures into which they are inserted.

As far as the heart itself is concerned, the papillary muscles undoubtedly play the most important rôle in propagating the murmur of mitral insufficiency to the apical regions. On the other hand, this fact alone might not have much clinical significance, since various structures lie normally between the heart and the chest-wall. It is perfectly conceivable that the systolic blow heard about the apex on the thorax may be due in greater part to the transmission of the loud murmur always present around the auriculoventricular junction in regurgitation to this area by the intervening tissues.

If this be true, then the presence or absence of the papillary muscles, so far as their rôle of transmission is concerned, would have but little influence on the clinical findings at the mitral area on the chest. But, if it were possible to remove the papillary muscles (as carried out, for example, in Experiment 3 B, still preserving the relations of overlying tissues to the heart, and if a material decrease in the intensity of the murmur over the structures about the apical regions were discovered, it is justifiable to conclude that the papillary muscles do have a clinical significance for murmurs audible at the apex.

EXPERIMENT 15.—The anterior and posterior papillary muscles removed as in Experiment 3, B. The current entered the aorta. A lung, arranged to cover the entire heart, furnished the intervening tissue.

Observations.—A very marked decrease in the murmur was noted at the area corresponding to the apical regions of the heart. Whereas, in the preliminary observations, before the removal of these muscles, the murmur at the apex was somewhat louder than that heard over the vicinity of the auriculoventricular junction—undoubtedly due to a greater thickness of the lung in this region—in the second set of observations made after the removal of the papillary muscles, the murmur heard over the apical regions was exceedingly less than that over the auriculoventricular junction. At this latter area it showed no appreciable change in intensity.

The definiteness of these results makes it clear that the papillary muscles are the principal factors in conducting the mitral regurgitant murmur to the regions about the apex. If the overlying tissues do play any part in conducting the murmur from the auriculoventricular junction to the chest-wall, it is so slight as to be negligible.

EXPERIMENT 16.—The right ventricular wall was removed. As in a former preparation, the anterior papillary muscle was transplanted to the interventricular septum and securely fastened in such a manner that it covered an area on the septum corresponding in extent to that on the wall from which it had been removed. The relations of lung to heart in the preceding experiment were reproduced here.

Observations.—The loudest murmur noted on the lung could be heard directly over the apex. In marked contrast to this, the areas above this region showed an abrupt decrease in intensity. The remaining area from which the papillary muscle had been removed showed a definite lessening of the murmur. Comparing the second chart of this experiment with the preliminary chart, it became apparent that the murmur over the apex had remained practically unchanged.

The results here corroborate former findings in three respects, namely: (1) the papillary muscles, whatever their location, furnish the principal medium for transmission of mitral murmurs to the apex (vide Experiments 10 and 11); (2) removal of these muscles from their normal sites results in a diminution of the murmur over the areas corresponding to their original locations (vide Experiments 10 and 11); (3) the structures in apposition to the heart-wall play no essential rôle in augmenting the sounds heard at the mitral area by conducting murmurs from the auriculoventricular junction (see Experiment 15).

As yet, no direct experimental evidence has been brought forth to explain why the murmur of mitral insufficiency is so often heard in the left axilla. Hirschfelder[9] offers the plausible explanation that it is due to the proximity of the anterior papillary muscle to this region. In view of the results of the experiments completed up to this point, such an assumption appeared to be correct. To settle this question definitely, Experiment 16 was repeated on another heart. *Intra vitam*, the heart is separated from the bell of the stethoscope in the axilla by lung and chest-wall. Were the chest-wall the essential factor in bringing the insufficiency murmur to this region, by transmitting it from the mitral area,

then it is reasonable to suppose that the murmur would be transmitted equally in all directions from the mitral area. Since this is obviously not the case, the lung must be regarded as the organ of propagation from the heart to the left axilla.

EXPERIMENT 17.—The anterior papillary muscle was transplanted to the septum, and a left lung placed over the heart, reproducing as nearly as possible the normal relations.

Observations.—The murmur heard over the lung in an area corresponding to the axilla showed a marked decrease in intensity in comparison to the one observed in the same region previous to the papillary transplantation. But the sound heard through the lung over the upper part of the left ventricle and over the auriculoventricular junction remained practically unchanged.

This confirms the assumption that the anterior papillary muscle is chiefly responsible for the murmurs heard clinically in the left axilla.

Having convinced ourselves that the papillary muscles play important rôles in the transmission of mitral insufficiency murmurs to the apex in hearts with normal musculatures, the question arose as to their real significance in pathological conditions.

Zielonko[15] and later Goldenberg[16] showed by microscopical measurements of normal and diseased hearts that hypertrophy of the wall is accompanied by a corresponding hypertrophy of the papillary muscles. Recently, this has been corroborated by the careful work of Gutch.[17]

That hypertrophy is a very frequent finding in pathological states of the heart is well known. Tangl,[18] and Romberg and Hasenfeld[19] as well, have shown that not only is it observed in persons in the most depraved state of health, but that in animals also, the condition develops even when they are enormously emaciated.

We feel justified then in assuming that the papillary muscles play rôles, in conduction of the insufficiency murmur, practically as important in the pathological heart as in the normal.

SUMMARY

1. The two papillary muscles play the most important rôle in the transmission of the insufficiency murmur from the mitral valve to the apex.

2. The transmission of the murmur toward the apex apparently depends only in small part on the thickness of the ventricular wall.

3. The papillary muscles must be intact to conduct the murmur.

4. The papillary muscles conduct regurgitant murmurs to whatever portions of the heart they may be attached.

15. Zielonko: Virchows Arch. f. path. Anat., 1875, lxii, 29.
16. Goldenberg: Virchows Arch. f. path. Anat., 1886, ciii, 125.
17. Gutch: Jour. Path. and Bacteriol., 1901, vii, 327.
18. Tangl: Virchows Arch. f. path. Anat., 1889, cxvi, 432.
19. Romberg and Hasenfeld: Archiv. f. exper. Path., 1897, xxxix, 341.

5. The vertical direction of the fibers of the papillary muscles accounts in great part for the conduction of the murmur by these structures.

6. The chordæ tendineæ transmit the murmur from the mitral segments to those portions of the heart into which they may be inserted.

7. If the tissues intervening between the heart and the chest-wall play any part in conducting a murmur from the auriculoventricular junction to the mitral area, it is so slight as to be negligible.

8. The murmur heard in the left axilla in mitral regurgitation is evidently due to the proximity of the anterior papillary muscle to that region.

We wish to express our sincere thanks to Dr. Hirschfelder for presenting this problem and for suggesting the feasibility of this method of investigation. To Professor Barker we are grateful for encouraging research, on our part, at this time.

TETANUS

E. W. HILL, M.D.
COLON, C. Z.

In considering the subject of tetanus we are struck by the fact that it is a disease that has been recognized for centuries, widely diffused throughout the world, found during all periods of life save the first five years, excepting the primary month; varying in mortality, age incidence, occurrence during the season of the year, and susceptibility of the sexes; a disease having an extensive literature, the data of which as to frequency, mortality, and prognosis are singularly indefinite and unsatisfactory, giving rise to conclusions and statistics both unreliable and confusing. The error, according to my judgment, is due in large part to the persistent disregard of certain clinical characteristics and natural tendencies of the disease as exhibited in incubation, progress, and duration, unmodified by any treatment whatsoever.

Recovery from tetanus once developed is to-day, as in the past, due more to the character of the attack than to the remedies employed.

Consecutive data of actual mortality, covering a long period of years, and a large number of cases confined to the same geographical area, should present information as to frequency, age, sex, season of the year, and modification by climate, if any.

Tetanus is comparatively a rare disease, due probably to peculiar biologic and chemical properties of its bacillus.

In the two great classes into which tetanus can be divided, tetanus of the tropics and tetanus of the temperate zones, all the clinical forms of the disease appear, but with marked differences which will be noted in their proper places.

TETANUS IN TEMPERATE ZONES

FREQUENCY

In the temperate zone of the United States the most frequent geographical locations, according to Anders and Morgan, are along the Hudson River Valley, Brooklyn and surrounding districts, Long Island, southern Pennsylvania, Virginia, Georgia, about Savannah, St. Louis, Illinois, Indiana and southern California, with a strip of land in New Jersey, 5 miles long and 1 mile wide, where the disease is endemic. In the New England states, the records that I have collected do not show any particular preference as to frequency in proportion to the population of one place over another, save that it is less common along the northern

border. In Mexico no essential difference appears in the character of the disease from that seen in the southern states of the Union.

In Massachusetss, comprising a geographical area of 8,266 square miles with an estimated population of 3,003,680 persons, from 1857 to 1908 — fifty-one years — there were 1,958,107 deaths from all causes, and from this total but 1,288 were due to tetanus, or one death from tetanus in every 1,520. From 1841 to 1908, 1,461 deaths from tetanus are recorded. Assuming a mortality of 75 per cent., 365 recoveries occurred, or a total of but 1,826 actual cases of tetanus in this area in sixty-seven years. This represents 0.007 per cent. of the total death-rate. For the years 1909 and 1910, fifty-two deaths can be added to the record, giving a sum total of 1,513 in sixty-nine years, tabulated as follows:

TABLE 1.—TETANUS IN MASSACHUSETTS

From	1841	to 1856	172	deaths
"	1857	" 1884	585	"
"	1885	" 1905	670	"
"	1906	" 1910	76	"
"	1857	" 1908	1,288	"
"	1841	" 1910	1,513	"

In a much larger area in the following eighteen states of the Union, viz.: California, Colorado, Connecticut, Indiana, Maine, Maryland, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, North Dakota, Vermont, Washington, and Wisconsin, containing an aggregate estimated population of 48,776,895 persons, or 55 per cent. of the total population of the United States:[1]

1. During the year 1909 there were 732,528 deaths from all causes with 1,373 deaths from tetanus, or one death in every 533 deaths from all reasons. Assuming an average mortality of 75 per cent. would give 343 recoveries and a total of 1,716 cases during the year, or one case in every 28,424 living persons. Of all tetanus recorded during the year, 422 cases, or 30.7 per cent., were in children under 1 year of age and appeared in the total death-rate of persons under 12 months (140,057), once in every 331, while from the beginning of the second year onward to 80 and over, once in 623 total deaths.

2. In a twenty-year period in England from 1889 to 1908 there were 2,124 deaths from tetanus, 1,623 of these in the seven-year period from 1902 to 1908. An average in the annual death-rate from all causes and at all ages to a million living persons in the seven-year period of but fourteen deaths from tetanus per million. While tetanus cannot be considered as a frequent menace to a community in the temperate climes, in a record of 140 different disease-representing fatalities, tetanus as a cause of death is outranked by ninety-two more frequent maladies. In

1. Bureau of Census, 1909.

fact, a person stands over eighty-three times as much chance of dying from tuberculosis, and fifty-three times from violence alone, as he does of succumbing to lockjaw. It is the high mortality-rate once acquired and the frequent relation to traumatic injuries that lends the disease its terrors. In 36,302 accidents and injuries occurring later than 1 year of age, as far as data could be obtained, tetanus followed as a complication once in every thirty-eight cases. This ratio does not apply solely to the casualties incident to the celebration of the Fourth of July, where blank cartridge injuries cause three out of four cases.

The lesions resulting from an infection by the specific bacillus of tetanus are preeminently those of nervous tissue. The ratio of disease in 90,374 deaths, classed as diseases of the nervous system, is shown in Table 2 and represents a frequency of but 0.6 per cent.

TABLE 2.—90,374 DEATHS FROM DISEASES OF THE NERVOUS SYSTEM

Name	Number	Per cent.
1. Cerebral diseases other than insanity	43,913	48.59
2. Paralysis, spinal	20,201	22.35
3. Convulsions	17,594	19.46
4. Epilepsy	5,076	5.62
5. Insane	2,903	3.22
6. Tetanus	585	.65
7. Chorea	102	.11
	90,374	100.00

A graphic portrayal of the annual line of mortality of 1,288 cases of tetanus, for a consecutive period of fifty-one years, notwithstanding our tremendous advance as to etiology and pathology, shows that modern treatment, save as to prevention, has failed to reduce the mortality.

TABLE 3.—RATIO OF TETANUS TO TOTAL DEATHS FROM ALL CAUSES FOR A PERIOD OF FIFTY-ONE YEARS IN MASSACHUSETTS

Years	Ratio	Increase
1903-1908	1 to 1,120	...
1898-1903	1 to 1,600	460
1893-1898	1 to 1,385	265
1888-1893	1 to 1,705	585
1883-1888	1 to 1,870	750
1878-1883	1 to 1,520	400
1873-1878	1 to 2,080	960
1868-1873	1 to 1,592	472
1863-1868	1 to 2,345	1,225
1857-1863	1 to 2,235	1,115

Moreover, almost without exception, for fifty years an increased death-rate one year has been followed by a sharp decline the following year or the one thereafter, and *vice versa*. These fluctuations in the same geographical space and under practically the same atmospheric and local conditions cannot, at present, be accounted for, but they do occur and must be considered in any estimate as to increasing or diminishing

frequency. Thus, in 2,024 deaths from tetanus in England, already referred to, from 1889 to 1901 — a period of thirteen years — but 501 are recorded, or 38.5 deaths per year, when, suddenly and without apparent reason, they increased to 201 per year and continued at this average for the next seven years, to 1908.

In Massachusetts the actual ratio per thousand total deaths has maintained a nearly steady increase as compared with a preceding period. Grouped in periods of five years, the record is seen in Table 3.

These facts admit of only these conclusions:

1. Tetanus is increasing in virulency and frequency.

2. There has been a reduction in total mortality from other diseases, especially the contagious and infectious.

3. Our present clinical treatment is not any more successful, save as to prevention, than when other methods (venesection and abstraction) were in vogue.

In all probability the latter two conclusions are correct.

CLIMATE

Climatic conditions modify the frequency of tetanus. It is more common with high temperatures; but cold, wet and dampness play a part. The weather records that I have examined seem to show that during the years of small precipitation and low humidity, the dry seasons, with moderate temperatures, are the years associated with diminished frequency.

In the United States the highest frequency and mortality are to be found in the summer months, especially after our national holiday,[2] July 4.

Since 1903, 33,075 persons have been maimed and injured, with 1,531 deaths; 901 of these deaths (58.85 per cent.), were due to tetanus; and in 983 cases of tetanus 796 (80 per cent.), resulted from blank cartridges, with only 187 from other causes.

A definite twenty-year record, from 1885 to 1905, of the climatic variations and frequency in 670 deaths from tetanus in Massachusetts, and the months in which they occurred, is seen in Table 4.

Nearly 69 per cent. (68.81), or 461 cases, occurred during the hot season from May to October, with but 209 cases, or 31.19 per cent., during the colder period from November to April. Over 63 per cent. of the 461 cases from May to October are recorded in June, July and August, and 48.29 per cent. of these in July alone. It is three times as frequent (3.07) in June, July and August as January, February and March. In

2. For a complete period of the last seven years see the summary published in The Journal Am. Med. Assn., Sept. 19, 1909.

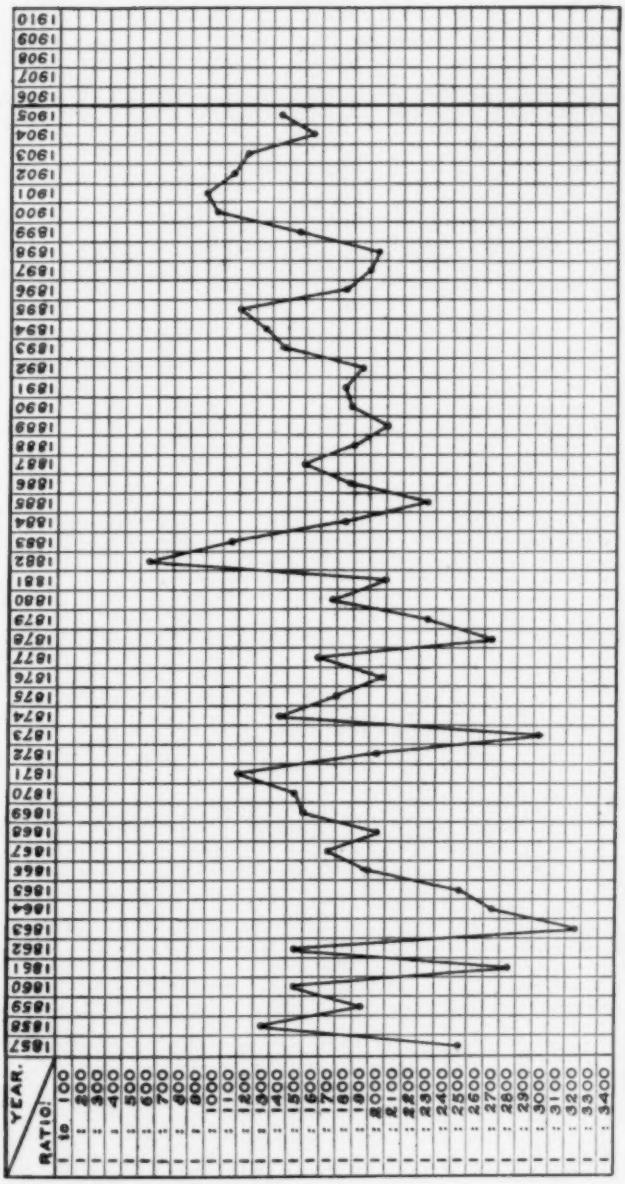


Fig. 1.—Chart showing tetanus mortality 1857-1905; ratio of deaths to total deaths from all causes in Massachusetts.

March, tetanus is the least frequent; in July, the most frequent. A careful analysis of records where the influence of July 4 could be excluded still shows July to have the highest record of the year.

TABLE 4.—FREQUENCY OF TETANUS IN THE VARIOUS MONTHS OF THE YEAR

Rank	Months	No. Cases	Per cent.
1	July	141	21.04
2	August	80	11.94
3	June	71	10.60
4	September	62	9.25
5	October	60	8.95
6	May	47	7.02
7	November	40	5.97
8	December	38	5.68
9	January	37	5.52
10	April	36	5.37
11	February	30	4.48
12	March	28	4.18
Total	12 months	670 cases	100.00

	Cases	Per cent.
Six months, May to October, inclusive	461	68.81
Six months, November to April	209	31.19
Three months, June, July, August	292	43.58
461 cases May to October.		
June, July and August	292	63.34
July alone	141	48.29

SEX

In temperate zones the disease is more common in males.

In 325 cases, including deaths and recoveries, 258 patients were males and sixty-seven females, a ratio of 3.85 to 1.

In the mortality record of the 670 cases, there were 510 male to 160 female patients — a ratio of 3.19 to 1.

Anders and Morgan reported 981 cases in which there were 778 male patients and 203 female, or 3.83 to 1.

This preponderance of the male sex has been explained as due to exposure. This cause cannot obtain in cases under 1 year of age where the males predominate in temperate zones at the ratio of 5 to 3 in any total number. In 504 deaths from tetanus in infants under 3 months taken from a seven-year period,[3] 1902-1908, 325 were male patients and 179 female, not quite two (1.81) male patients to one female.

In 2,124 cases[4] there were 1,598 male to 526 female patients, or 3.04 to 1 — a rather low average.

3. Williams: Brit. Med. Jour., July 2, 1910, p. 51.
4. England Registrar General's Reports, 1889-1908.

The combined totals in these cases represent 4,100 cases of tetanus, as follows:

Number	Male	Female	Ratio
325	258	67	3.85 to 1
670	510	160	3.19 to 1
981	778	203	3.83 to 1
2,124	1,598	526	3.04 to 1

with an average ratio of 3.29 male patients to 1 female.

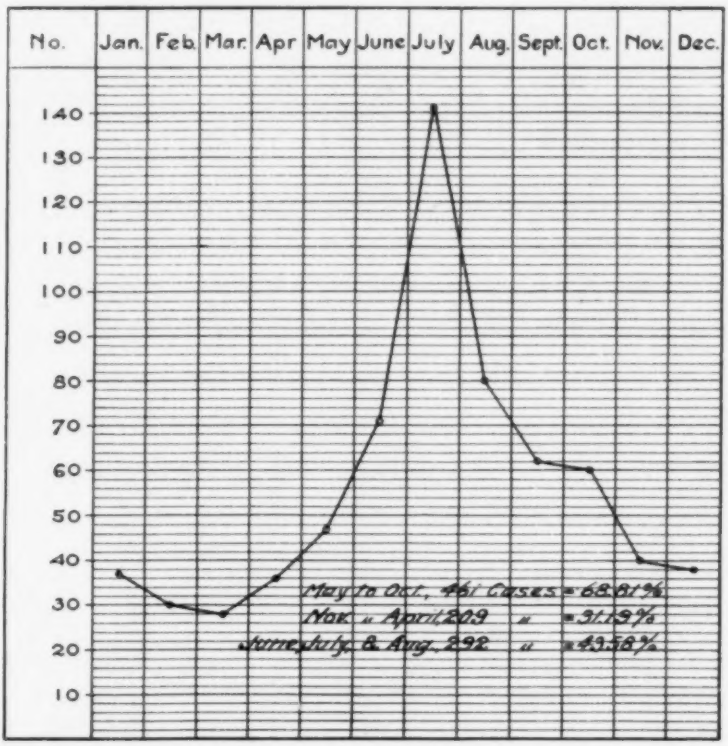


Fig. 2.—Chart showing frequency of tetanus in Massachusetts (670 deaths 1885-1905). Twenty years total death line by months.

The ratio rises at certain ages. Thus, during the period of greatest frequency, from 10 to 40 years of age in 185 cases, the average ratio was 5 (4.97) to 1, and in 105 cases occurring from 10 to 20 years of age nearly 10 (9.50) male patients to 1 female are recorded.

The relative frequency in the sexes at the different ages of life in 325 cases is seen in Table 5.

TABLE 5.—TETANUS, MALES TO FEMALES, TEMPERATE ZONE—325 CASES

Age	Male	Female	Ratio
Under 1 year	15	9	1.66 to 1
1 to 5 years	3	2	1.50 to 1
5 to 10 "	23	7	3.29 to 1
10 to 15 "	59	8	7.38 to 1
10 to 20 "	95	10	9.50 to 1
20 to 30 "	37	12	3.08 to 1
30 to 40 "	22	9	2.44 to 1
40 to 60 "	46	11	4.18 to 1
60 to 80 "	17	7	2.43 to 1
10 to 15			7.38 to 1
10 to 20			9.50 to 1
10 to 40			4.97 to 1

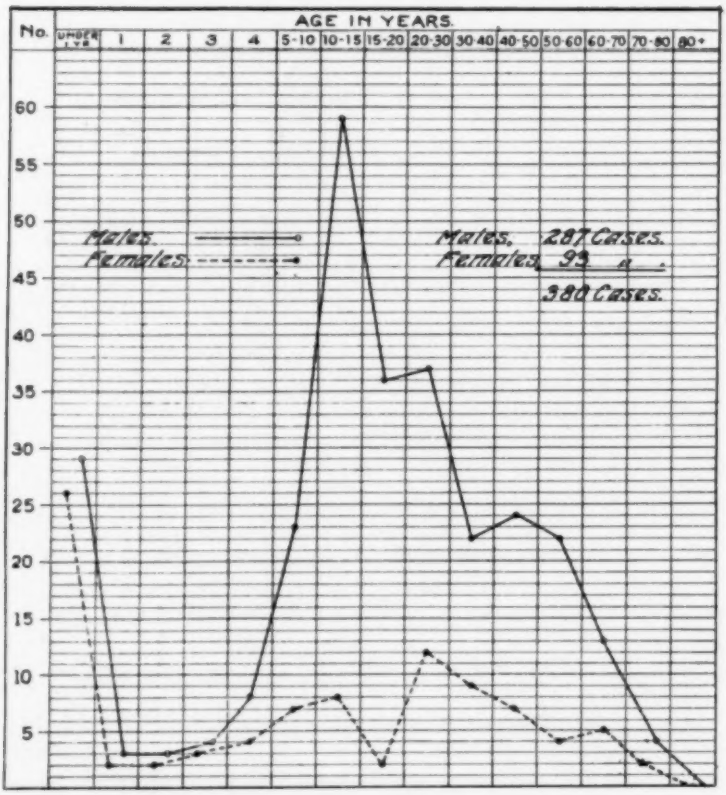


Fig. 3.—Chart showing ratio of males to females at different ages in New England States.

AGE

One of the remarkable characteristics of this malady is the varying prevalence at certain periods of life, as shown in Table 6, which represents 3,038 cases of tetanus, and a record of the respective ages at which

they occurred. The data do not essentially modify the record in 1,000 cases, previously reported by me, save as to a much larger percentage under 1 year of age. As these cases cover a long-continued period of time with a wide geographical and populous area, they should furnish a basis from which a pretty correct estimate can be made.

TABLE 6.—RESPECTIVE AGES OF LIFE IN 3,038 CASES OF TETANUS

Age	No. of Deaths	Per cent.
Under 1 year	678	22.31
1 to 5 years	110	3.62
5 to 10 "	303	9.97
10 to 15 "	479	15.76
15 to 20 "	257	8.45
20 to 40 "	641	21.09
40 to 60 "	399	13.13
60 to 80 "	171	5.67
Total	3,038 cases	100.00
1 to 10 years	413	13.59
10 to 20 "	736	24.23
20 to 40 "	641	21.09
1 to 20 "	1,149	37.80
10 to 40 "	1,377	45.32

It will be seen that, with a few exceptions, cases occurring in the first ten years of life, excluding the primary month, appear after the fifth year.

In the above table, 22.31 per cent. developed under 1 year of age. From 1 to 5 years of age tetanus is very rare, 110 cases, or 3.62 per cent. are listed. Many of the reported cases of tetanus with recovery in children from 2 to 5 years, a period when tetanus is conspicuous by its absence and when diarrheas and marantic conditions are common, are not tetanus at all, but tetany, 24 per cent. of which appears at this time and is most common in March and April.

It is not easy to explain the relative infrequency during these early years. It would seem that among children learning to walk, with the frequent falls, contusions and small lacerated wounds, infection would be particularly common. The line reaches its height during the 15 to 20-year period and from 25 falls rapidly and steadily. Diminishing as old age approaches, tetanus still appears late in life; Yandell reports one case at the age of 89.

In any period of five years the largest number appeared from 10 to 15 years with 479 cases and 15.76 per cent. From 1 to 20 years we find recorded 37.80 per cent., and if we include patients under 1 year — 60.1 per cent. — of the entire number. From 20 to 40 years, 21.09 per cent. occur and from 40 to 60 years, 13.13 per cent. Nevertheless, 171 (over 5.5 per cent.) are present in the period from 60 to 80 years (nearly 7 per cent. [6.94] in the record of 1,000 cases). Even at this time, tetanus is more common, nearly twice in a smaller record, than during the first five years of life.

From the data in these 3,000 cases it would appear that tetanus in a temperate climate reaches its height around 15 years of age, while in the thirty-year period from 10 to 40, over 45 per cent. (45.32) in this record, of all cases occur (50.90 per cent. in 1,000 cases).

Considered as traumatic and idiopathic tetanus, with all patients under 12 months of age excluded, of all cases from the second to the

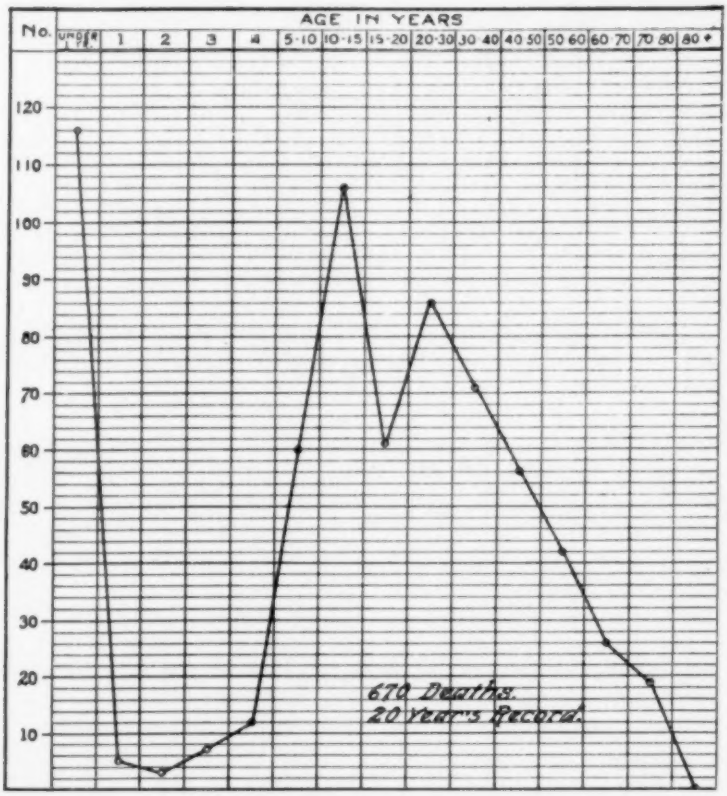


Fig. 4.—Chart showing frequency of age in tetanus patients in Massachusetts.

eightieth year of life and over, nearly 59 per cent. (58.34) are present in this thirty-year period.

Table 7 presents a continued record for twenty years in one locality, giving the age, number and per cent. in the mortality record of 670 cases, and a one year's record (1909) in eighteen states having 55 per cent. of the population of the United States.

TABLE 7.—MORTALITY RECORD COVERING TWENTY YEARS IN ONE LOCALITY, AND ONE YEAR IN EIGHTEEN STATES

Massachusetts, Twenty Years Ages in 670 Deaths from Tetanus			U. S. Census Report, One Year 1373 Deaths from Tetanus in 1909		
Age, Years	No.	Per cent.	Age, Years	No.	Per cent.
Under 1	116	17.31	Under 1	422	30.70
1 to 5	29	4.33	1 to 4	47	3.50
5 to 10	60	8.94	5 to 9	153	11.10
10 to 15	106	15.82	10 to 14	200	14.57
15 to 20	61	9.10	15 to 19	97	7.03
20 to 30	86	12.84	20 to 29	121	8.80
30 to 40	71	10.60	30 to 39	126	9.20
40 to 50	56	8.36	40 to 49	87	6.30
50 to 60	40	5.98	50 to 59	63	4.60
60 to 70	26	3.88	60 to 69	43	3.10
70 to 80	19	2.84	70 to 79	13	1.00
			80	1	.10
	670	100.00		1,373	100.00

For a comparison with tropical records Table 8, a summary with all cases, under 1 year of age excluded, is given:

TABLE 8.—2,360 CASES OF TETANUS IN TEMPERATE ZONE. UNDER 1 YEAR EXCLUDED

		Per cent.
1 to 10 years	413	17.50
10 to 20 "	736	31.18
20 to 40 "	641	27.12
1 to 20 "	1,149	48.79
10 to 40 "	1,377	58.34

TROPICAL TETANUS

If we turn our attention to tropical and semitropical countries tetanus presents marked differences in frequency, variety, age, sex, and period of the year, as compared with colder climates; but to what degree and under what conditions has been little understood, resulting in erroneous and exaggerated statements.

FREQUENCY

The disease is well understood to be more frequent here than in temperate zones, especially in certain localities. If we consider it as a whole, regardless of variety in any total number of cases, my data confirm this opinion; other things, however, must be considered. One of the striking features of life in tropical countries is the terrible mortality of children from general and especially convulsive diseases. In temperate zones, 86 to 87 per cent. of tetanus is of the traumatic and idiopathic variety, occurring from 5 to 80 years of age. On the other hand, 86 to 87 per cent. of tetanus in the tropics occurs under 1 year of age and includes tetanus neonatorum.

TETANUS IN THE ISLAND OF JAMAICA

In a period of seventeen years in this island there were 272,287 deaths from all causes, of which 1,038 were due to tetanus. One death was from tetanus in every 262 (262.32) deaths — nearly six times as frequent (5.79) as in the United States.

In 1905, an average year, there were 19,503 deaths. Of these, 76.85 per cent. were in children under 5 years of age, or 14,989; 5,597 or 37.34 per cent. in children under 1 year; 9,392, or 62.66 per cent., in children from 1 to 5 years. But sixty-three deaths from tetanus at all ages occurred this year; forty-four from tetanus neonatorum, nineteen traumatic and idiopathic.

The increased frequency of tetanus, due to the overwhelming percentage of tetanus neonatorum, will be seen by the following: In the seventeen-year period from 1891 to 1908, already referred to, with 1,038 deaths from tetanus recorded, 83.62 per cent. or 868 were from tetanus

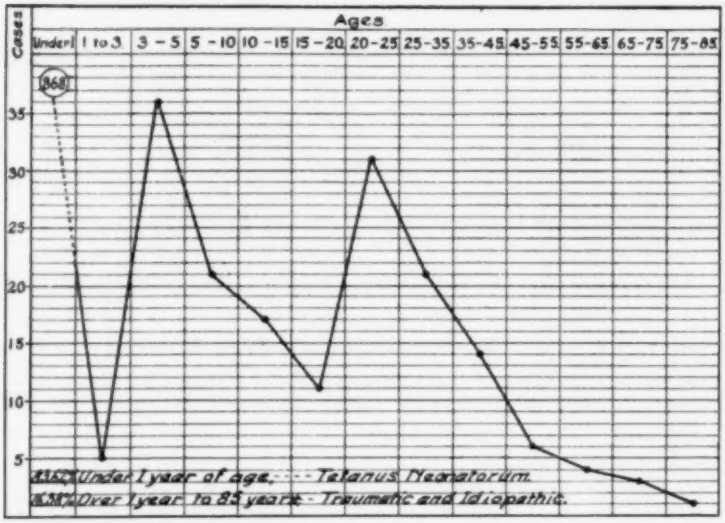


Fig. 5.—Chart showing seventeen years' record (1,038 cases) of tetanus in Island of Jamaica.

neonatorum, and but 170 or 16.38 per cent. from traumatic and idiopathic tetanus. During this period 466,343 births occurred, 62 per cent., or 289,164 illegitimate; 80 per cent., or 373,074, unattended. There was one death from tetanus in every 537 births.

We find that in seventeen years, traumatic and idiopathic tetanus appeared as a cause of death but once in 1,602 deaths from all causes, approximately the same ratio as in the area of New England.

If the ratio of total deaths in 1909 in the United States is considered, 1 to 662, it is less than half as frequent in Jamaica.

Traumatic and idiopathic tetanus in warm countries appears to reach its height in an earlier period of life — around 5 and from 5 to 10 years,

instead of from 15 to 20, as in colder climes. This will be readily seen by a comparison of the summaries with one year excluded. From 5 to 10 years of age, tetanus is almost twice as common in tropical islands as in temperate zones (36.47 per cent. against 17.50 per cent.), whereas in the 10 to 20-year period, nearly exactly the reverse is true — 16.47 per cent. for the tropics to 31.18 per cent. in colder latitudes.

TABLE 9.—AGES IN 1,038 CASES OF TETANUS, SEVENTEEN YEARS' RECORD, JAMAICA

Age in Years	No. of Cases		Per cent.
Under 1	868	Tet. Neon.	83.62
1 to 3	5	" Traum.	.....
3 to 5	36	" "	.....
5 to 10	21	" "	.....
10 to 15	17	" "	.....
15 to 20	11	" "	.....
20 to 25	31	" "	.....
25 to 35	21	" "	.....
35 to 45	14	" "	16.38
45 to 55	6	" "	.....
55 to 65	4	" "	.....
65 to 75	3	" "	.....
75 to 85	1	" "	.....
	1,038		

UNDER ONE YEAR, 83.62 PER CENT. TETANUS NEONATORUM. CASES UNDER ONE YEAR EXCLUDED. TROPICAL RECORD

	Per cent.
1 to 10 years	36.47
10 to 20 years	16.47
20 to 40 years	34.71
1 to 20 years	53.94
10 to 40 years	51.24

CUBA

Cuba presents conditions similar to those in Jamaica, although tetanus is more frequent. Twelve years' record in Havana, 2,909 deaths from tetanus, of which number 87.49 per cent., or 2,545, were from tetanus neonatorum and 364, or 12.51 per cent., were of traumatic and idiopathic origin. In the year 1901, in Havana, 5,720 deaths are recorded, 4,169 white, and 1,551 colored. One hundred and forty-eight cases of tetanus occurred during the year, ninety-one white and fifty-seven colored, which would be one death from tetanus in every thirty-nine (38.65) deaths; or by races, one white in every forty-six (45.74), and one colored in every twenty-seven (27.21), a high mortality-rate. As in Jamaica this is not due to traumatic and idiopathic tetanus. Of these 148 cases, 86.49 per cent., or 128, were tetanus neonatorum, and only twenty, or 13.51 per cent., belonged to the traumatic and idiopathic variety. This is an average of one death from traumatic and idiopathic tetanus in every 286 deaths during the year, which is five and one-half (5.43) times more frequent than in temperate zones. We find also in these 5,720 deaths from all

causes that 1,453, or nearly 26 per cent. (25.40) were in children under 1 year of age. This would give a death from tetanus neonatorum in less than every twelve (11.35) births. Also 5,721 births are recorded with a death from tetanus neonatorum in every forty-five (44.69) deliveries.

A twelve-year record of the mortality of tetanus in Havana is shown in Table 10.

TABLE 10.—2,909 CASES, HAVANA, CUBA—TWELVE YEARS' RECORD

Year	Tetanus Neonatorum	Trau. and Idiop.
1890	355	28
1891	320	31
1892	256	26
1893	282	41
1894	173	30
1895	180	31
1896	232	31
1897	215	28
1898	173	19
1899	92	32
1900	139	46
1901	128	21
	2,545	364

Tetanus neonatorum, 2,545 cases; 87.49 per cent.
Traumatic and idiopathic, 364 cases; 12.51 per cent.

In the Bertillon classification of this period (179 diseases) tetanus as a cause of death, regardless of variety, ranks ninth in frequency in Cuba, but with the exclusion of infantile tetanus it descends to eighty-sixth in the scale.

It will be seen in the foregoing data that tetanus in the tropics is about five and a half to six times as common as in colder climates, but only a small percentage of the disease is due to the traumatic and idiopathic variety, less than 14 per cent. In nearly 4,000 cases (3,947), 86.47 per cent. belongs under tetanus neonatorum, or 3,413 occur in infants, and is directly preventable if proper means are employed, while only 534 cases were of the traumatic and idiopathic variety, or 13.53 per cent.

Tetanus neonatorum is not entirely a disease of the tropics. One thousand, three hundred and seven cases occurred in Michigan, Illinois, Pennsylvania, Maryland, District of Columbia, Louisiana and intermediate states.

In a ten-year period in Louisiana there were 806 cases of tetanus; 79.8 per cent., or 642, were tetanus neonatorum, and only 164, or 20.2 per cent., were traumatic and idiopathic tetanus. Tetanus neonatorum also appears in frigid zones. In the island of Heimaey, near Iceland, nearly all the children died at one time, the population being kept up by immigration.

INFLUENCE OF TEMPERATE CLIMATES IN GENERAL

We do not observe the marked predominance in certain months of the year as in colder climates. In 1,068 cases (thirty additional cases), from January to March, the greatest number is recorded, with October to December the smallest, as follows:

	Cases
January to March	299
April to June	285
July to September	262
October to December	222
	1,068

We should note that the greatest number occur in the dry season, also the fact that but three months in temperate zones, June, July and August, approximate the temperature range of the tropics. In seventeen years' record during these three months in the area of Massachusetts, 248 cases are recorded. For the same period of the year in Jamaica, 273 cases are found.

SEX

The equality of the sexes suffering from tetanus in the tropics is noteworthy. Of 868 cases of tetanus neonatorum, 440 were males and 428 females. In 170 cases of traumatic and idiopathic tetanus, eighty-three were males, and eighty-seven females, the females predominating.

TETANUS ON THE CANAL ZONE

Tetanus on the Canal Zone is tetanus in a tropical country modified by modern methods of sanitation and aseptic technic. It is peculiar in the relative proportion of the sexes and the small percentage of children, as compared with other tropical countries. Practically the records of Ancon and Colon hospitals represent the history of tetanus on the Isthmus, all cases of the disease on the line being transferred to one of these points.

Since the American occupation in 1904, to January, 1910, 107,511 cases of disease have been admitted to these hospitals, with 3,418 deaths. Of these admissions twenty-five were cases of tetanus, a frequency of .0.0024 per cent. There were twenty-one deaths and four recoveries, a mortality of 84 per cent. At Colon Hospital there were fifteen cases, with thirteen deaths and two recoveries, and at Ancon Hospital, ten cases with eight deaths and two recoveries. There were twenty-one males and four females, a ratio of 4.20 to 1, practically the ratio seen in the United States. This is not the true tropical ratio of tetanus and is due to peculiar local conditions. In the twenty-one males there occurred seventeen deaths and four recoveries. Of the four females all died.

The incubation periods of eight were undetermined. The average incubation of fatal cases was eight days, nineteen hours. The average incubation of recoveries was fourteen days, twelve hours. The average duration of fatal cases was six days, fourteen hours. The average duration of recoveries was thirty-four days. The shortest incubation was two days, the longest thirty days. The shortest duration was twenty hours, the longest fifty-seven days. Of the total cases eighteen were acute, four subacute, two chronic, and one puerperal.

No patient with acute tetanus recovered. The puerperal case was quickly fatal. Of the recoveries two were subacute and two the chronic form of the disease. Only thirteen of the patients were employees on the canal. Of the remaining twelve, two were admissions by request of the Alcalde, and ten were Zone charity cases.

TABLE 11.—TETANUS ON THE ZONE, 1904 TO 1910, TWENTY-FIVE CASES*

Nationality	Sex	Age	Color	Month	Incub.	Days Duration	Terminat.	Variety
Martinique	M	21	B	Jan.	21	4 days 7 hrs.	Death	Acute
Jamaica	M	17	B	Jan.	11	21 days	Recov.	S. Acute
Martinique	M	26	B	Jan.	2	8 days	Death	Acute
Italian	M	26	B	Feb.	9	4 days 18 hrs.	Death	Acute
Jamaica	F	32	B	Feb.	Undet.	5 days	Death	Acute
Panama	M	69	B	March	9	4 days	Death	Acute
Jamaica	F	28	B	March	Undet.	20 hrs.	Death	Acute
Jamaica	F	34	B	April	6	20 hrs.	Death	Acute
Panama	M	22	B	May	10	21 days	Recov.	S. Acute
Grand Cayman	M	55	B	June	7	9 days	Death	Acute
Panama	M	40	B	June	Undet.	3 days 12 hrs.	Death	Acute
Jamaica	M	28	B	June	Undet.	3 days	Death	Acute
Panama	M	13	B	July	3	26 hrs.	Death	Acute
American	M	37	W	July	18	3 days 12 hrs.	Death	Acute
Trinidad	M	20	B	Aug.	Undet.	21 days	Death	S. Acute
Hayti	M	23	B	Sept.	7	2 days	Death	Acute
St. Vincent	M	35	B	Sept.	8	6 days	Death	Acute
Jamaica	M	26	B	Sept.	4	10 days	Death	Acute
Grenada	F	20	B	Sept.	6	4 days	Death	Acute
Jamaica	M	23	B	Oct.	Undet.	7 days	Death	Acute
Columbian	M	12	B	Oct.	30	57 days	Recov.	Chronic
Jamaica	M	21	B	Nov.	7	37 days	Recov.	Chronic
Jamaica	M	40	B	Nov.	14	12 days	Death	S. Acute
West Indies	M	28	B	Nov.	Undet.	2 days	Death	Acute
Jamaica	M	50	B	Dec.	Undet.	4 days 12 hrs.	Death	Acute

Twenty-five cases, twenty-one deaths, four recoveries—mortality, 84 per cent.

*A classification has been established that tetanus under ten days is acute and over is sub-acute. The standard should be based on duration and not on incubation of the disease.

When we remember the former black record of the Isthmus as to disease, and consider the multitude of lacerated and septic wounds of the hands and feet since 1904 treated on the line; wounds favorable to development of tetanus bacilli; and also the constant use of high explosives with the death of only one American from tetanus in six years, we must conclude that not only does it speak well for the medical and sanitary methods used, but it also emphasizes the fact that tetanus can be pre-

vented in tropical countries, proper methods being employed, as well as in temperate zones, the average on the Isthmus being a trifle over four cases a year.

Tetanus with an incubation period of fifteen days, with death resulting in thirty-six to forty-eight hours, the attack once developed, is as acute and severe as that manifested with an incubation of six to eight days.

THE DISEASE IN GENERAL

PROGNOSIS

Hippocrates stated that "such persons as are seized with tetanus die within four days or if they pass these they recover." A lapse of 2,400 years and all our modern methods and advanced technic but little modify this statement. Published data so far have been unreliable for two reasons:

1. Reports of any groups of cases in which the clinical history of incubation and duration of the disease are ignored, are of no value whatever.

2. In individual reports from this or that operator of success with some particular treatment, only the favorable cases find their way into print.

As stated by Lambert, the ratio of death is in direct proportion to the length of the incubation period and severity of the infection, but in my opinion the statement fully as important should be added, that the prognosis and rate of mortality is definitely modified by the duration of the disease regardless of treatment.

Our prognosis should always be guarded. Recoveries in tetanus occur more from the character of the attack than the remedies employed, nevertheless, recovery is possible to-day as in the past both from disease and treatment. The case of LaFrancs, who was bled nineteen times and made the acquaintance of 772 leeches and weathered the storm, is no isolated exception of therapeutic wandering in the history of this malady.

Tetanus is a most treacherous disease. Death occurs when the patient is apparently on the high road to recovery and restoration to health when all hope has passed away.

INCUBATION

The modification of the prognosis by the length of the period of incubation has received much attention. It has been assumed that the higher mortality rate following a brief incubation period is due to increased virulency of the bacillus causing the attack. This conclusion is hard to deny or affirm.

In Table 12 the record of the incubation in 1,092 cases of tetanus is seen to be from one to twenty days. Cases over twenty days' incubation are not included, as they form but a small percentage of the total number, and represent a large proportion of the recoveries.

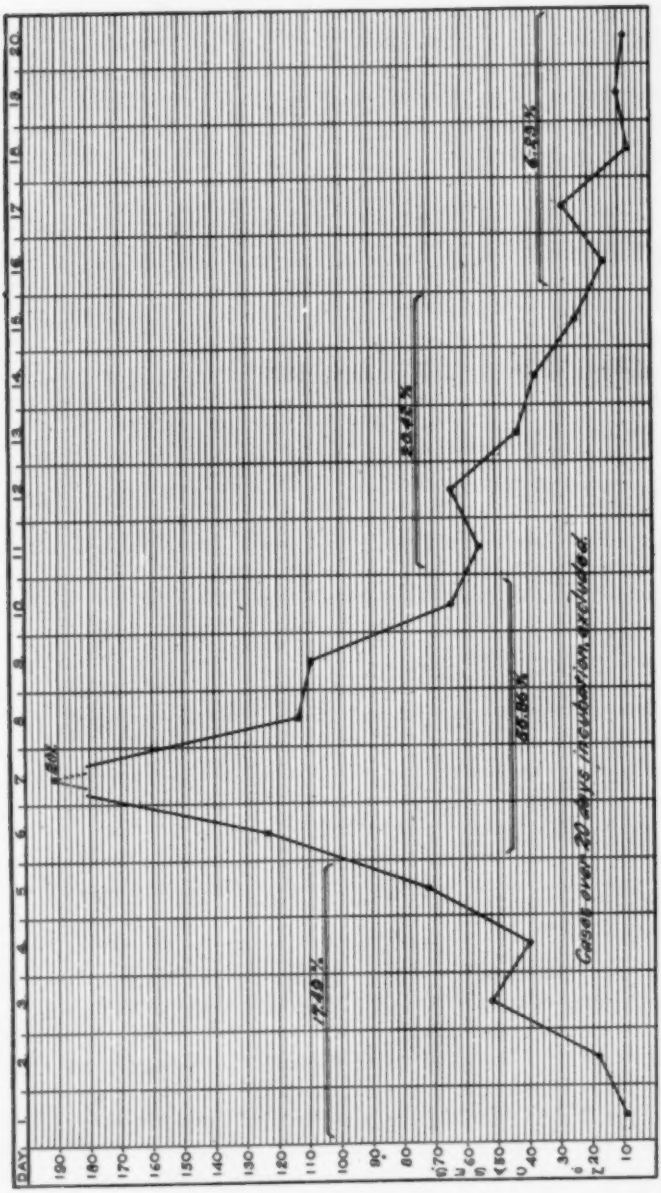


Fig. 6.—Chart showing incubation in 1,092 cases of tetanus.

TABLE 12.—INCUBATION IN 1,092 CASES OF TETANUS

Days	No. of Patients		Per cent.
1	9		.....
2	18		.....
3	52		.....
4	40		.....
5	72	1 to 5 days	17.49
6	123		.....
7	201		.....
8	113		.....
9	109		.....
10	64	5 to 10 days	55.86
11	55		.....
12	64		.....
13	43		.....
14	37		.....
15	24	10 to 15 days	20.42
16	15		.....
17	28		.....
18	7		.....
19	10		.....
20	8	15 to 20 days	6.23
Total	1,092		

1 to 5 days, 191—17.49 per cent. Acute tetanus, 1 to 10 days, 801—73.35 per cent.

5 to 10 days, 610—55.86 per cent.

10 to 15 days, 223—20.42 per cent. Subacute tetanus 10 to 20 days, 291—26.65 per cent.

15 to 20 days, 68—6.23 per cent.

6 to 9 days, 546—50 per cent. Largest number on seventh day, 201 cases.

DURATION

The duration of the disease has not received the attention that it merits as modifying the prognosis. In all reports of the reduction of mortality by a specific form of treatment, it should always be considered.

In 1,264 cases of tetanus, lasting from one to twenty days, the duration was as follows:

Acute Tetanus: 1 to 5 days, 574 or 45.41 per cent.; 5 to 10 days, 423 or 33.47 per cent.; 1 to 10 days, 997 cases, 78.88 per cent.

Subacute tetanus: 10 to 15 days, 177 or 14 per cent.; 15 to 20 days, 90 or 7.12 per cent.; 10 to 20 days, 267 cases, 21.12 per cent. Total, 1,264 cases, 100 per cent.

We find on the third and seventh days the largest number of cases.

The modification of the prognosis by the duration of the disease will be seen in Table 13.

During the first five days an average mortality of 81.18 per cent. occurred.

From the fifth to the tenth day the prognosis improves about 4 to 5 per cent. (4.33), the mortality being 74.47 per cent. Not until the tenth day is there any material reduction. Somewhere between the tenth and eleventh days the line of recovery crosses the death-line and the patient

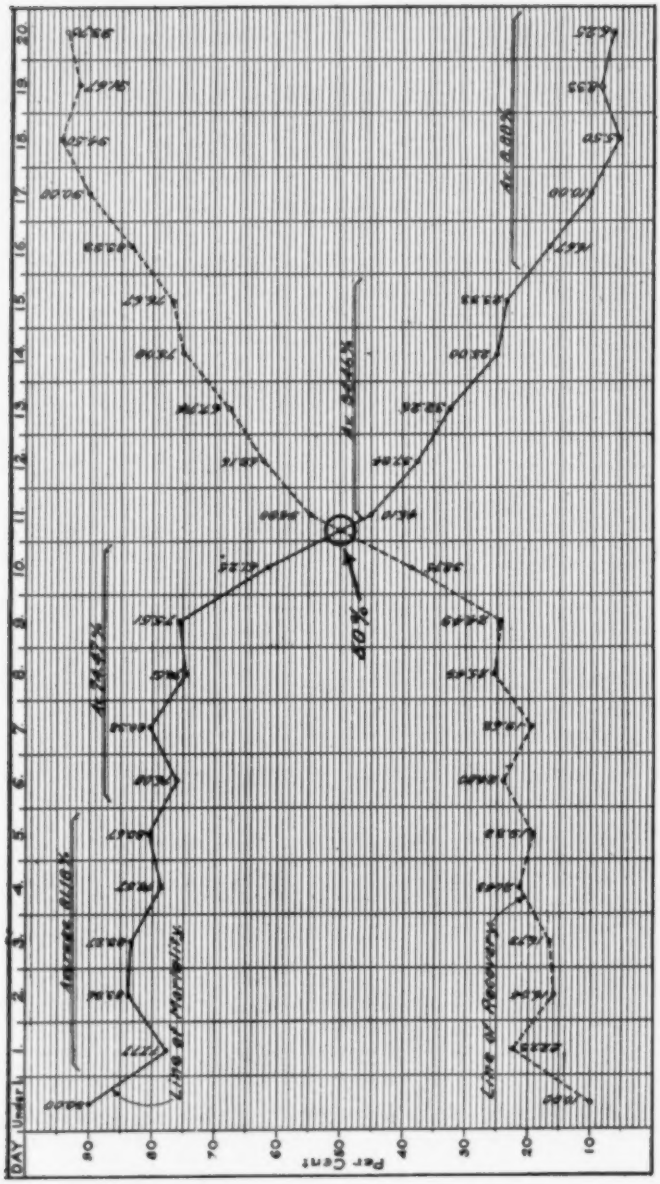


Fig. 7.—Chart showing duration and mortality as to duration in 1,364 cases of tetanus.

has an even chance for life. On the tenth day of duration the mortality falls to 50 per cent. From this point the prognosis improves steadily to the fifteenth day, about 6 per cent. every twenty-four hours, the average mortality recorded for these five days being 34.46 per cent. From the fifteenth day onward the prognosis improves more rapidly, less than 9 per cent. (8.88) of deaths occur in cases with a duration from fifteen to twenty days. In cases extending from twenty to twenty-five days and over, it is often difficult to state the exact time of termination of the disease. Cases with this long duration represent, as with long incubation period, a large percentage of the recoveries. In 126 cases of this character 120 recoveries occurred and but six deaths, a mortality of 4.76 per cent. In 165 cases of Anders and Morgan, twenty days and over, there were 152 recoveries and thirteen deaths.

TABLE 13.—MORTALITY OF TETANUS AS TO DURATION OF THE DISEASE—1,264 CASES

Days	Total	Deaths	Recovered	Mortality Per cent.
Under 1 day	10	9	1	90.00
1	72	57	15	77.77
2	106	89	17	83.96
3	141	116	25	83.27
4	126	99	27	78.57
5	119	96	23	80.67
6	75	57	18	76.00
7	158	127	31	80.38
8	61	45	16	74.51
9	49	37	12	75.51
10	80	49	31	61.25
11	51	23	28	45.10
12	37	14	23	37.84
13	31	10	21	32.26
14	28	7	21	25.00
15	30	7	23	23.33
16	24	4	20	16.67
17	20	1	19	10.00
18	18	1	17	5.50
19	12	1	11	8.33
20	16	1	15	6.25
Total	1,264	850	414	.....
1 to 5 days	574	466	108	81.18
5 to 10 days	423	315	108	74.47
10 to 15 days	177	61	116	34.46
15 to 20 days	90	8	82	8.88
Acute tetanus, 1 to 10 days	997	781	216	78.32
Subacute tetanus, 10 to 20 days	267	69	198	25.85

SUMMARY

Days	Incubation 1,094 Cases Per cent.	Duration 1,264 Cases Per cent.	Mortality ..... Per cent.
1 to 5 days	17.49	45.41	81.18
5 to 10 days	55.86	33.47	74.47
10 to 15 days	20.82	14.00	34.46
15 to 20 days	6.23	7.12	8.88
1 to 10 days	73.35	78.88	78.32
10 to 20 days	26.65	21.12	25.85

The more brief the incubation and duration, the higher is the mortality. The longer the duration the greater is the chance of recovery. The prognosis is better if trismus exists alone for a few days. Spasms extending to the trunk are serious symptoms, also elevation of temperature. The erratic temperature seen in this disease has been considered of no great moment, nevertheless it is of value in the prognosis. Temperature rising above 104 F. on or before the fifth day, even if not preagonal, practically always indicates a fatal termination. In 1,201 cases but two recovered with hyperpyrexia. It is very rare with a favorable issue. A sudden fall of a septic temperature to 1 or 2 degrees below normal, in a case in which infection from tetanus bacilli has been probable, often pre-

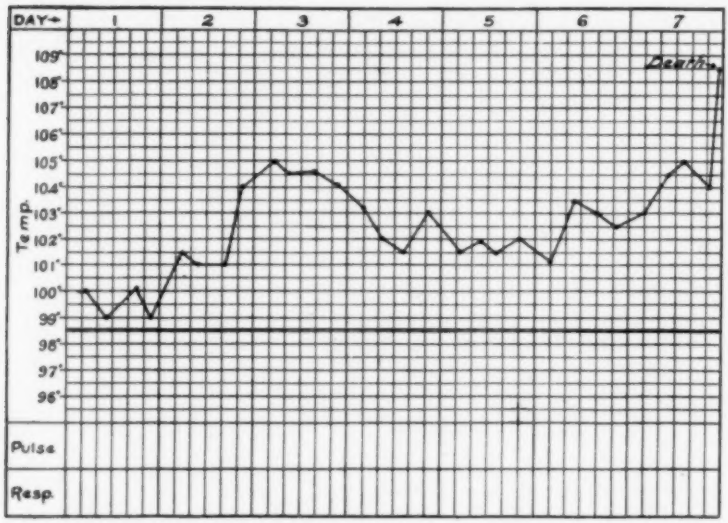


Fig. 8.—Chart showing temperature in a case of acute tetanus. Male patient, aged 40; splinter in foot. Incubation, 6 days; duration, 7 days. High temperature average; termination fatal. Treatment: morphin, bromid, chloral, antitoxin.

cedes the development of tetanic symptoms, and its occurrence should be regarded with suspicion even if no symptoms of tetanus are then present. Temperature falling once, having risen, does not improve the prognosis as in ordinary febrile diseases. It is impossible to state the exact process involved. Incidentally, some of the highest known temperatures, 114 F. and over, appear in this disease after death, falling in an hour or so.

Relative changes in the pulse — respiration — temperature ratio — are observed with these erratic fluctuations, viz., 140 pulse, 24 respiration, 97 temperature; or 50 pulse, 40 respiration, 108 temperature, etc.

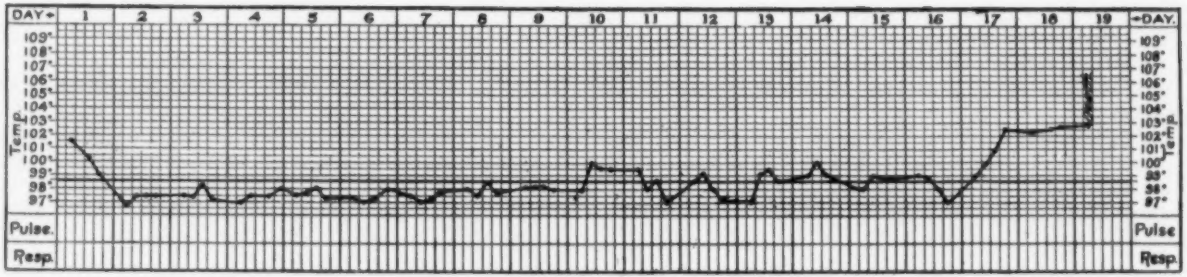


Fig. 9.—Chart showing temperature in a case of subacute tetanus. Malepatient, aged 20; leg ulcer (?). Incubation, nineteen days; duration, nineteen days. Subnormal temperature average; termination fatal. Treatment: antitoxin (intramuscularly), bromid and chloral.

Marked dissociation of pulse, respiration and temperature from the normal relation, especially with arhythmia and falling volumes, are always grave, and, appearing before the fifth day of duration, indicate a severe infection and a fatal termination, though the end be delayed.

Profuse sweating is a clinical feature, while inaction of the sweat glands and kidney secretions are dangerous symptoms, likewise aspiration pneumonia, which may appear suddenly.

Notwithstanding the prolonged muscular tension little metabolism is believed to occur; albumin seldom appears in the urine; creatin and creatinin are not found.

Idiopathic Tetanus.—The data as to this variety are unsatisfactory. It is assumed to be more fatal in hot countries than in temperate climates.

Mental aberration and delirium are not typical of an attack of tetanus, and indicate exhaustion, method of treatment or complications.

Diminished severity of a convulsion is of less value than an increased interim between them as indicating improvement.

BLOOD-CHANGES

The modification of the prognosis by the blood-picture is at present doubtful. But few records have been published with reported cases.[5] In two fatal cases Cabot found hemoglobin to be 75 per cent. and, according to the same author, eosinophils are not diminished as in other fevers. The cases presented here raise some question as to this conclusion.

In eleven cases — nine deaths and two recoveries — the leukocyte and differential counts were as follows:

The following cases were observed at Colon Hospital:

CASE 1.—Male, aged 40; subacute; fatal; incubation fourteen days; duration twelve days; splinter in foot; negative malarial parasites.

Days of Disease	Leukocytes	Differential	Per cent.
First	11,000	Polynuclear	56
Sixth	13,600	Large mononuclear	35
		Small mononuclear	7
		Eosinophils	1
		Mastzellen	2

CASE 2.—Male; marked uncinaria; aged 69; acute traumatic; fatal; incubation nine days; duration three days twelve hours; nail in foot.

Days of Disease	Leukocytes	Differential	Per cent.
Second	5,800	Polynuclear	81.
		Large mononuclear	5
		Small mononuclear	8
		Eosinophils	6
		Unclassified	3

5. Brown, one case, fatal; leukocytes, 13,000. Quoted in Osler's Modern Medicine, iii. Cabot, two cases, fatal; leukocytes, 11,000, 11,900, 19,000, 19,000. Cited in Cabot's Clinical Examination of the Blood, Edition 5.

CASE 3.—Male; aged 42; chronic tetanus; incubation unknown; duration thirty-seven days; recovery; leg ulcer, small; positive malaria E. A.

Days of Disease	Leukocytes	
Second	5,200	No differential
Fourth	8,300	
Sixth	10,000	

CASE 4.—Male; aged 36; acute tetanus; fatal; incubation three days twelve hours; duration one day twelve hours; lacerated wound of foot; gangrene; amputation.

Days of Disease	Leukocytes	Differential	Per cent.
First	11,600	Polynuclear	83.67
	11,400	Large mononuclear	10.33
		Small mononuclear	5.9
		Eosinophils	.1

CASE 5.—Male; aged 10; acute traumatic tetanus; incubation ten days; duration sixteen days; recovery; splinter in foot; negative malaria.

Days of Disease	Leukocytes		Differentials per cent. Second	Fourth	Sixth	Seventh	Eighth	Eleventh
Second	13,600	Polyn.	56.2	84.9	83.3	87.3	83.2	81.2
Fourth	18,100	Large	10.4	7.3	5.3	5.7	5.4	4.2
Sixth	15,000	Small	25.2	7.4	10.37	5.7	10.6	13.8
Seventh	13,000	Eosinoph.	.7.	.4	.3	.3	.0	.2
Eighth	14,000	Unclass.	1.4	.0	.3	.0	.8	.4
Eleventh	14,000							

CASE 6.—Male; aged 30; acute; fatal; incubation ten days; duration eight days twenty-one hours; crushed foot; amputation; negative malaria.

Days of Disease	Leukocytes		Differentials per cent. Third	Fourth	Fifth	Eighth
Third	27,000	Polynuclear	90.4	83.5	91.4	73.4
Fourth	11,800	Large	4.3	4.	3.7	5.4
Fifth	17,300	Small	4.9	10.6	3.8	17.4
Eighth	11,800	Eosinoph.	.26	.3	.4	2.4
		Mast cell	.26	.0	.2	.4
		Basop.	.0	.3	.0	.0

CASE 7.—Male; aged 10; acute traumatic tetanus; fatal; incubation five days; duration two days nineteen hours. Thigh amputation and thumb; complicating septicopyemia.

Days of Disease	Leukocytes	Differential	Per cent.
First	58,000	Polyn.	81.7
		Large	6.
		Small	11.2
		Eosinoph.	.7

CASE 8.—Acute traumatic tetanus; male; Barbadian; aged 24; incubation eight days nineteen hours; duration one day nineteen and one-half hours; lacerated toe.

Days of Disease	Leukocytes	Differential	Per cent.
First	7,400	Polyn.	82.2
Second	14,200	Large	11.8
		Small	7.2
		Eosinoph.	.0

Twenty-six leukocyte counts and fourteen differentials. In ten out of eleven cases (Case 7 not included for obvious reasons), with twenty-five leukocyte counts, give an average of 13,200. In the hospital Cases 1, 2, 3, and 5, two deaths and two recoveries, leukocytosis can hardly be claimed as due to the wound, as will be seen from the above histories. In these cases, eleven leukocyte counts register an average of 12,366, and nine differentials, polynuclears 77.47 per cent.; large 9.88 per cent, small mononuclears 10.44 per cent., eosinophils 1.7 per cent., unclassified, etc., 1.4 per cent.

As to eosinophils: In one case at Colon Hospital in two counts of 1,000 cells not a single eosinophil was present. In the cases recorded above, the average was diminished. Case 2 with 6 per cent. cannot be considered as typical on account of the marked complicating uncinariasis. In Case 5, count made shortly after admission, 7 per cent. were found with no uncinaria or other complications; forty-eight hours later with steadily rising average daily temperature but 0.4 per cent. were found, falling to 0.3 per cent. on the sixth and seventh days with none at all on the eighth (temperature 103.5), and but 0.2 per cent. on the eleventh day.

Thirteen counts in these six cases — five deaths and one recovery — from the first to the eleventh day of the disease, excluding the first day of Case 5, give an average eosinophilic record of 0.49 per cent. Tabulated below:

Eosinophils	Per cent.	Days of Disease
Case 1	1.	First
Case 2	6.	Second, uncinaria
Case 4	.1	First
Case 5	7.	On admission, second day
	.4	Fourth
	.3	Sixth
	.3	Seventh
	.0	Eighth
	.2	Eleventh
Case 6	.26	Third
	.3	Fourth
	.4	Fifth
	2.4	Eighth
Case 7	.7	First
Case 8	.0	First

TETANUS ANTITOXIN

This is at once a specific and a failure. Under whichever head it falls will depend on *when* it is used and the *method of its administration.*

Its failure should be readily understood. Here we are dealing with a germ whose spore is extremely resistant, a toxin whose virulence is appalling with man, the animal most sensitive to it. Of the Berger and Cohne toxin 0.00005 mg. will kill a mouse, but 0.0023 mg. is necessary to destroy a man weighing 175 pounds, as compared with 30 to 100 mg. of strychnin.

Dried pus from a tetanic horse is active after sixteen months, and earth containing spores and bacilli, after eighteen years. Splinters after fifteen years are virulent. Its spore resists water, at 80 C. an hour; phenol (carbolic acid) 5 per cent., ten hours; and bichlorid solution, 1-1,000, three hours.

Bacteria are not homogeneous bodies. Their molecules differ biologically. Their toxins do not unite with a nerve-cell in the same manner as alkaloidal poisons like strychnin, whose union with a nerve-cell is a loose one, from which it can be obtained with solvents, such as ether, chloroform, etc. Tetanus toxin is most firmly joined. It is taken into the nerve-cell to become a part of it. It is assimilated in the same manner, by chemical processes, that food materials are and cannot be obtained from it by solvents. It becomes an integral part of the protoplasm.

Tetanus toxin is absorbed by the motor nerves alone. Tetanus antitoxin is absorbed by the lymph and the blood as generally administered. Laboratory experiments have not informed us as to the precise action of the antitoxin, and Ehrlich's side-chain hypothesis has been valiantly used to explain the resultant condition in the economy. Tetanus antitoxin has not shown any power to dislocate poison once united with the protoplasm.

Administered immediately on injury it has proved a specific both in veterinary and human medicine. Kocher even states that any physician should be subject to reproof who fails to use it following street and infected injuries. Care should be exercised in the variety of the serum and method used. Villard reports thirty-one cases following the prophylactic use of the serum. The standard unit in the United States since 1907 is that the immunity unit shall be ten times the least quantity of antitetanic serum necessary to protect a 350 gm. guinea-pig for ninety-six hours against the official test dose of toxin furnished by the laboratory of the P. H. and M.-H. Service. One hundred and fifty units per cubic centimeter is the least that is now offered for use. The prophylactic dose should be certainly 1,500 units or 10 c.c. of any such standard preparation.

Its value decreases with every minute of elapsing time. The various methods of administration have been, subcutaneous, intravenous, intracerebral, subarachnoid, intraneural and spinal.

Subcutaneously it is slowly absorbed. The maximum amount does not appear in the blood for twenty-four hours, the greater portion being eliminated unchanged by the secretions, milk, feces, and urine. It is not taken up by the nerve-substance at all.

When given intravenously it appears in the thoracic duct in a few minutes. In spite of this it must be borne in mind that two minutes after a fatal dose of the toxin, twice as much antitoxin is necessary as would have been required if given simultaneously; eight minutes later,

ten times as much; and ninety minutes, forty times; and so on. To lose twenty-four hours where minutes mean death is not sound medicine, even if the remedy were of known value.

Subarachnoid injections do not affect the toxins in the cord as far as is known. Whether used subcutaneously, intravenously, or subdurally, the antitoxin finds its way to the lymph and the blood, there to destroy only that part of the poison remaining in the wound, or which is circulating in the blood to attack other motor nerve plates. In all probability tetanus toxin is a compound body — tetanospasmin producing the clinical tetanic phenomena of the disease — and tetanolysin destroying certain erythrocytes, and whose molecular structure resembles that of diphtheria toxin in having a combining haptophore group for antitoxin, and another, or toxophore group.

The intracerebral method has no rationale whatever and adds a serious shock to conditions already desperate. This is plainly evident if the lymph circulation of the cerebrum is considered at all. The active drainage apparatus for the effete plasma being briefly as follows:

In the walls of the cerebral vessels between the muscularis and the adventitia exist the Virchow-Robin lymph spaces carrying plasma from the blood-vessel walls along the course of the vessels to the lymph lacunæ of the pia. A subsidiary system of little value to nervous tissue. The active drainage apparatus consists of two varieties of neuroglia cells. One wedge-shaped lying just beneath the perindyme, the horse-hair cells with branches lying on the free surface of the cortex. The other more important are the pedasteroid — those myriads of peculiar cells with fleshy bodies and channeled feet, which take up the waste fluids and solids and empty into the perivascular lymph spaces of His. These at least have a selective action, as after cerebral hemorrhage we find them filled with detritus of red blood-corpuscles, and after acute toxemias such as alcohol, ricin, etc., are swollen and disintegrating.

The His perivascular lymph space empties directly on the epicerebral surface, from which point through the lymph slits of Arnold it finds its way through the pial lymphatics and eventually through the foramina at the base of the skull by the deep cervical lymphatics into the thorax.[6]

Tetanus antitoxin administered by the intracerebral method simply arrives at the same point as in other methods, and is not absorbed by the nerve substance, the process being equivalent to purifying a reservoir by sterilizing the mouth of a stream.

By the intraneural method antitoxin must stand or fall. It must be injected directly into the nerve plexuses leading from the wound, into the hypoglossal and spinal accessory, into the cauda, even into the cord itself between the sixth and seventh vertebræ. The cauda must be injured

6. Berkley: Abstract in Johns Hopkins Hosp. Bull., June, 1909.

to obtain results. Keen hints at a laminectomy for this purpose. Reliable statistics at present concerning this remedy after symptoms have appeared are, to say the least, discouraging.

The careful statistics of Jacobson in 203 cases, in which all the methods described were used, gave a mortality of 80.7 to 93 per cent. in the acute cases, and 32 to 50 in the subacute.

It is a matter of grave doubt if patients dying after fifteen days do not succumb as much from exhaustion as from the disease. An important method of eliminating this factor, scarcely mentioned in our textbooks, is related to the control of sensory impressions. The multitude of sensory impulses that pass over the nerves and in health register no impression and no motor response. In this disease they do produce such action. Here we have a direct motor and a reflex sensory tetanus.

A muscle contracted by a single stimulus will further contract by a series of stimuli. In the sensory cell itself a single stimulus may produce no response, while a series will call forth a reaction. A summation of stimuli occurs in the cell protoplasm. In health we recognize marked changes in a physiologically tired and exhausted neuron from one at rest. While it is not within the scope of this paper to discuss the intimate structure of a neuron, it should be noted that up to a certain point, recovery is possible for the neuron. Function is restored long before histologic changes have passed away and on distinctly similar lines as those observed in the acute toxemias, such as alcohol, ricin, bacillary infections, and diphtheria.

For the normal integrity of a neuron it should receive a normal peripheral stimulus, no more, no less.

In tetanus it is essential to produce sensory nerve-block not only to cells directly affected by the toxin, but also to protect cells not so directly affected, from receiving disordered stimuli resulting in perverted impulses and deranged metabolism. It is as important to prevent sensory impressions going in as to prevent motor ones coming out. Tetanus antitoxin should be used in every case of tetanus, but other methods that have proved of value in the past should not be neglected. Sulphate of magnesia is in no sense a specific for tetanus, but produces temporary relief from the paroxysms. Chloretone, the latest addition to the medicinal remedies advocated, is undoubtedly of value in this regard, perhaps the best to date. Free catharsis and the use of salt solution should not be neglected.

It is in preventive medicine that antitoxin finds its sphere. By its aid we can practically eliminate from our prognosis the presence of tetanus as a complication, not only in infected wounds, but in postoperative tetanus. It is well known that with the most careful surgical technic on concealed parts of the body, such as the intraperitoneal and rectal regions, this complication occurs. The literature of this variety is increasing. Peterson has recently collected records of 101 cases previous

to 1890, and forty-nine since. Others could be added; one case has occurred on the Isthmus at Santo Tomas Hospital, Panama. The ratio of peritoneal to non-peritoneal operations as to tetanus mortality remains nearly the same to-day as in the preantiseptic era. It is extremely fatal in all forms. The average mortality is over 86 per cent. and does not represent the true severity of the disease. In ninety-two cases, with an incubation of less than ten days there were four recoveries, a mortality of 96 (95.65) per cent.; fifty-eight of these occurred from the seventh to the ninth day after operation, with only one recovery. In fifty-four cases with an incubation from ten to twenty-five days, there were thirteen recoveries, a mortality of 76 (75.92) per cent. The average duration is likewise brief. In 124 cases, 117, or 94.35 per cent., lasted under ten days, and ninety-three, or 80 (79.49) per cent. of the 117 patients, died in the first three days of the disease. But seven cases had a duration of ten to twenty-five days. Antitoxin fails when the attack has once developed, as in other forms of the disease, as can be seen from the following:

Postoperative Tetanus, Thirty-Eight Patients Treated with Antitoxin

Incubation under ten days.....	23	Deaths 22	Recovery 1	Mortality 95.65
Incubation ten to twenty days....	15	Deaths 9	Recovery 6	Mortality 60.00

Postoperative Tetanus without Antitoxin

Incubation under ten days.....	59	Deaths 56	Recovery 3	Mortality 94.92
Incubation ten to twenty-five days,	38	Deaths 31	Recovery 7	Mortality 81.58

According to current reasoning this would prove, if it proves anything, that antitoxin is of no value under ten days and reduces mortality 22 per cent. in cases with an incubation of ten to twenty-five days. I know of no one with the temerity to seriously advance such a proposition. The only reasonable conclusion is that, as in other forms, the reduced mortality is due to the character of the attack and the length of incubation and the duration.

While this form of tetanus has followed the use of silk, silkworm gut, silver wire, kangaroo tendon and catgut, in the great majority of cases catgut has been used. In cases in which the peritoneum has been opened, the mortality has been much greater than following other operations. In 119 cases with peritoneal interference the mortality was 90.76 per cent. In thirty-one cases in which the peritoneum was not opened the mortality was 80.65 per cent.

In the twenty-one cases of Richardson, nineteen, or 90 per cent., followed peritoneal interference. In these cases catgut was used in the suture of the wounds. By the most searching methods of investigation no contamination was found in the catgut used. He reports that at the Royal Infirmary in 4,377 operations, of which 1,492 were intraperitoneal, no case of tetanus appeared with gut from the same source as used in the fatal cases. The attempt to prove that these cases all came from one

section in England, where there exists epidemically a disease of sheep known as louping ill, which presents all the symptoms of tetanus, and the presence in the abdominal cavity of a large bacillus resembling that of tetanus, has no standing with the profession.

It should be noted in this connection that for the development of the tetanus bacilli the presence of a mixed infection seems necessary, the presence of some aerobic organism that will consume the oxygen rapidly and allow the tetanus bacillus to develop. Development does not occur in healthy tissue.

Catgut has been conclusively shown to be infected, and still be negative to cultural tests. In twenty-four fatal cases, isolation of the bacillus was obtained in only eight.

Aside from catgut we should take into consideration facts usually overlooked. Living bacilli occur in 5 per cent. of healthy men, and up to 20 per cent. in hostlers, dairymen, etc. In the domestic and herbivorous animals such as the horse and cow, we find living tetanus bacilli, probably more virulent by their temporary stay, in the intestinal canal. Spores and bacilli can be inhaled or swallowed with dust; raw, uncooked vegetables, berries, and other fruits derived from manured and fertilized soil.

We can certainly diminish the frequency of this form of the disease as a complication, by using only catgut that has been autoclaved at 110 to 115 F. and the use of small sizes not over No. 3.

Other measures have been suggested, such as purgation, suppression of uncooked vegetables and fruits for several days previous to operation, the administration of antitoxin while the patient is still under the anesthetic. Such precautions seem to have a reasonable basis and are well worthy of trial.

ANTITOXIN AND CHLORETONE

I desire to report briefly four cases of tetanus treated at Colon Hospital with antitoxin and chloretone. The detailed reports of these cases will be made later by Dr. Brem, chief of the medical clinic.

CASE 1.—Acute tetanus; recovery. Male; white; aged 10; incubation ten days; duration sixteen days; splinter in foot.

On August 5, the patient ran a splinter into his foot; the wound was dressed and apparently healed in two or three days. Patient was first seen by me on August 17, at which time there was difficulty in opening and closing the jaws. Two days previously he had noticed some slight stiffness and pain on opening the mouth. He was immediately admitted to the hospital at 2:50 p. m. as a tetanus patient. The temperature on admission registered 102.5. Though apparently healed and hard to find, the place of injury was opened and a piece of tissue removed and wound thoroughly cauterized. A splinter was found imbedded in the tissue, over half an inch in length. Under ether anesthesia 3,000 units of antitoxin were given intraneurally into the sciatic nerve of the leg below the groin and 3,000 more intravenously by the median basilic vein of the arm. The symptoms continued to increase steadily with rigidity, convulsions, arching of

back, and rising daily average temperature and disassociation of the normal pulse and respiratory rhythm up to the tenth day of the disease. The condition of the patient at this time was decidedly serious. On the eleventh day (day beginning at 3 p. m.) the temperature had risen to 104.5 F., pulse 156, respiration 38, and remained with small change at this point until 4 a. m. when a marked change occurred for the better, the temperature falling 4.5 to 100 F., pulse 116, and respiration 24 per minute, the first material fall of temperature, pulse and respiration since the third day of the attack. The improvement in the general condition continued until on the sixteenth day the temperature touched normal, pulse 96, respirations 18. Decreasing stiffness and irritability continued for some days later. The last convulsion was recorded on the twelfth day. From the splinter were recovered classical tetanus bacilli, which caused tetanus in guinea-pigs. From the time of the ether anesthesia until the eleventh day, as occasion required, chloretone was given in solution by rectal enema in 30-grain doses. Complete relaxation followed each dose, lasting from eight to sixteen hours, during which time the patient slept quietly. Antitoxin was given daily subcutaneously in doses of 3,000 units. Liberal nourishment was supplied by nutrient enema and stomach tube feeding. Saline solutions with frequent laxatives to promote elimination by the skin and kidneys.

Seven leukocyte counts on various days gave an average of 14,600, and the differentials a diminished eosinophil percentage.

In the temperature chart the marked change between the tenth and eleventh day, almost in the nature of a crisis, should be noted and compared with the data and plan in the section on prognosis as to duration of the disease in the accompanying paper. (Chart 10. Temperature, pulse and respiration.)

Case 2.—Acute tetanus, traumatic. Male; colored; Barbadian; aged 34; machinist's helper; incubation ten days; duration eight days nineteen hours; fatal.

On August 9, at about 9:30 p. m., the patient's foot was crushed by an engine. On admission half an hour later, foot was amputated at tarsometatarsal joint. Sloughing of the flaps occurred five days later. August 20, ten days from injury, noticed some stiffness in opening and closing of the jaws. Under ether anesthesia 3,000 units of antitoxin were given intraneurally into the sciatic nerve of leg and 6,000 units intravenously in the basilic vein of arm. From this time daily 3,000 units antitoxin were given subcutaneously and, as symptoms required, chloretone in 60-grain doses by rectal enema. As in the previous case, relaxation followed promptly, continuing from eight to sixteen hours and even longer, the patient resting and sleeping quietly. Laxatives, salines, and nourishment as in Case 1. No amelioration occurred in the regular progress of the disease. The temperature, pulse and respiration continued more erratic until on the eighth day at 4 p. m. it stood at 104.5 F., pulse 140, respiration 40, with a general condition that indicated a fatal termination, which occurred the next day at 3 p. m.

Four leukocyte counts on various days from the second to the sixth gave an average of 17,000 and diminished eosinophils in the differentials. In this case no tetanus bacilli were obtained, or cultures from wound that produced tetanus in guinea-pigs.

The subnormal temperature on the ninth and part of the tenth day of incubation, a condition frequently seen in these cases previous to any symptoms of tetanus, may be noted in Chart 11.

Case 3.—Acute traumatic tetanus; fatal. Male; colored; Jamaican; aged 10; incubation five days; duration two days nineteen hours.

On November 23, the patient fell beneath a box-car, crushing left thigh and right thumb. Admitted at 10 p. m. Amputation of the thigh at lower third; thumb dressed. On November 29, five days after injury, he was very irritable to touch, sensitive to light, and cried out frequently as if in pain. The next morning the neck was stiff, abdominal muscles rigid and the back arched. The patient was removed to the operating room and the stump reamputated 4 inches above the old wound, with amputation of the thumb at first joint.

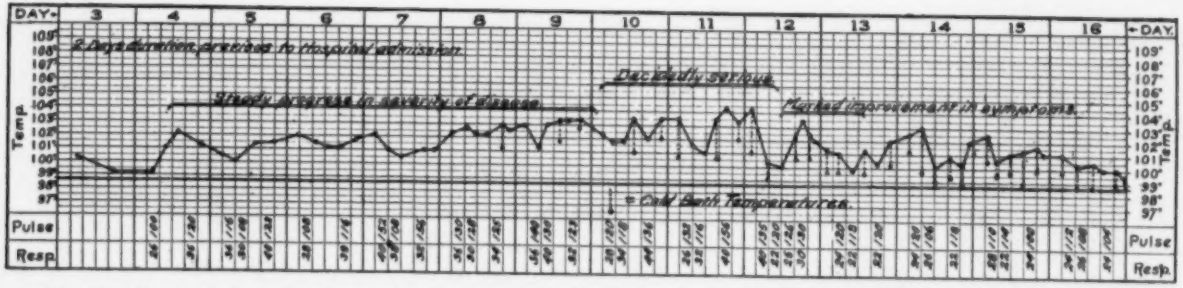


Fig. 10.—Chart showing temperatures in a case of acute traumatic tetanus. Male patient, aged 10, American. Incubation, ten days; duration, sixteen days, with recovery. Treatment: antitoxin (intraneurally, intravenously, intramuscularly), and chloretone.

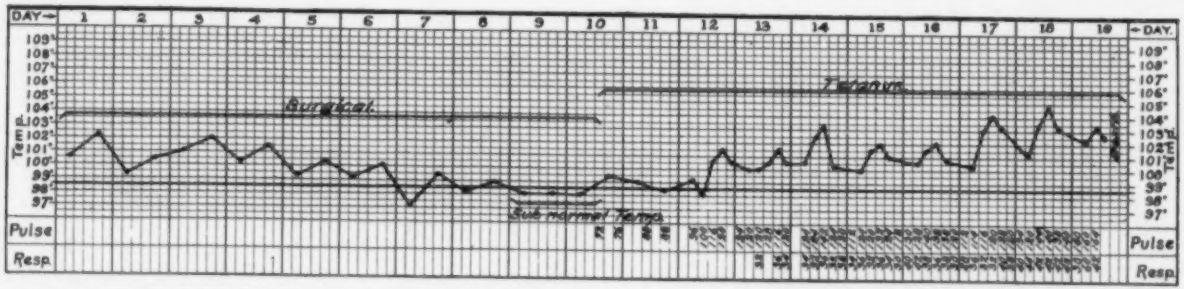


Fig. 11.—Chart showing temperature in a case of acute tetanus, terminating fatally. Male patient, aged 30, Barbadian. Crushed by engine; amputation of foot. Incubation, ten days; duration, eight days, twenty-one hours. Treatment: antitoxin (intraneurally, intravenously, intramuscularly), and chloretone.

Under ether anesthesia 6,000 units of antitoxin were given into the sheath of the sciatic nerve and 3,000 more intravenously into the median basilic vein. On recovering from the ether, 30 gr. of chloretone were given by rectal enema producing complete relaxation. An attempt was made six hours later to give antitoxin into the cervical cord but was unsuccessful; in lieu 6,000 units were given subcutaneously. On the morning of the 30th, twenty-four hours from the first symptoms of tetanus, the temperature was normal and pulse 80. Four hours later temperature was 101.4 F. and rising steadily (pulse 160), until at noon the next day it registered 105.3 F., pulse 168, respiration 42. Death occurred eight hours later at 8:45 p. m.

A leukocyte count twenty-four hours after first symptom of attack gave an average of 58,000, the differential showing 81 per cent. polynuclears, decreased eosinophils, 3 myelocytes, and 39 nucleated red blood-cells in 515 cells counted.

Large numbers of tetanus bacilli were recovered from the wound, which caused tetanus in guinea-pigs. At autopsy smears from multiple abscesses in the liver

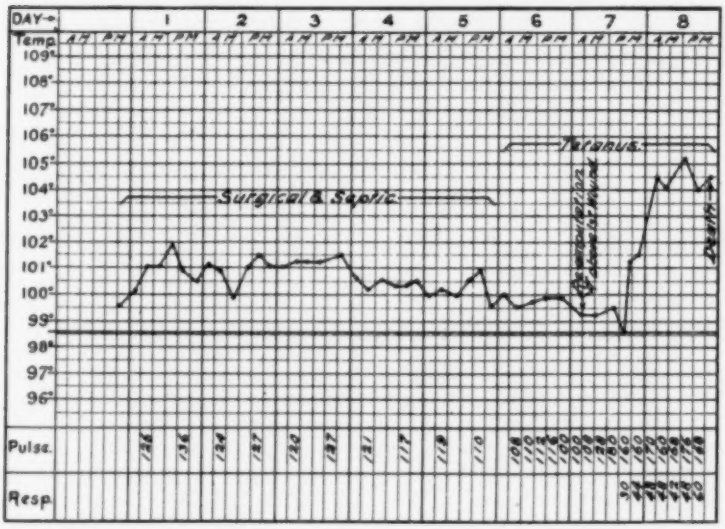


Fig. 12.—Chart showing temperature in a case of traumatic tetanus terminating fatally. Male patient, aged 10, Jamaican. Amputation, thigh and thumb. Incubation, five days; duration, two days nineteen hours. Treatment: antitoxin (intraneurally, intravenously, intramuscularly), and chloretone.

gave Gram-positive cocci in chains. While this case was acute with short incubation, the end was undoubtedly assisted by the complicating septic pyemia present.

CASE 4.—Male; aged 24, Barbadian, acute traumatic tetanus; fatal; incubation eight days and eighteen hours; duration one day nineteen and one-half hours; laceration of toe.

On February 25, at 11 a. m., the patient received an injury crushing the right little toe with small laceration of the surface. During the next five days he ran a small daily temperature averaging normal on the sixth and seventh days from injury. At 5 a. m. on the morning of the eighth day he complained of stiffness of the jaws. The temperature remained subnormal at 97 F. during forenoon. An intramuscular injection of antitoxin (3,000 units) was given immediately, and later the injured toe was amputated under ether anesthesia, with 3,000 units

of antitoxin in the sheath of the sciatic nerve in upper third of the thigh and 3,000 more intravenously in the basilic vein of arm. When he recovered from anesthesia, 60 gr. of chloretone were administered by rectal enema. The symptoms steadily increased, with rigid abdomen, arched back, frequent convulsions of the trunk muscles; exaggerated reflexes and a double Kernig present. Sixteen hours after previous injection (sciatic and intravenous), 6,000 more antitoxin units were given intravenously. The temperature rose steadily to 105.4 F., pulse 160 to 180 and respiration 32 per minute. Death occurred at 12:30 p. m., forty-three and one-half hours after first symptom of the disease.

From the beginning to the end there was at no time the slightest amelioration of the symptoms or halt on the progress of the disease. By three methods in twenty-four hours, 15,000 units of antitoxin were used; and in less than thirty hours, 150 gr. of chloretone by mouth and rectal enema and four hypodermics of ¼ gr. each of morphin without the slightest apparent effect in controlling convulsions or causing muscular relaxation save, possibly, as to some decrease in rigidity of the jaw muscles. Not even hypnosis was produced, the patient remaining conscious and able to answer questions and protrude the tongue up to an hour of decease. At autopsy the liver was cirrhotic. Cultures before and after death from the wound gave no tetanus bacilli, but small Gram-positive cocci, some in pairs, and large Gram-positive bacilli resembling air bacilli. Inoculation of guinea-pigs did not produce tetanus. Two leukocyte counts on first and second days gave 7,200 and 14,400 leukocytes. In the differentials no eosinophils were present.

Here are four cases of tetanus of acute variety — one recovery and three fatalities — in which chloretone was used to produce relaxation from muscular spasm and convulsions with an entirely successful result in this regard in three, and total failure in one. No deleterious action as to heart or respiratory centers, or interference with the functions of the skin and kidneys, was observed in any case.

It should be further noted that on the seventh day in Case 1, cold sponge baths were given at high temperature periods to assist in radiation and elimination. Theoretically, this procedure is contra-indicated as a stimulant to the sensory nervous system. These baths were given while the patient was under chloretone and the result as to the general condition was most happy for the time being. The effect on the temperature range was small up to the time of the change in the record between the tenth and eleventh days, from which point the fall was quite marked, at one time 3.5 degrees, the reduction lasting some time. Neither chloretone nor sulphate of magnesia can be considered as a specific for tetanus, but a part of symptomatic treatment.

The objections to sulphate of magnesia are: First, the technic of its use, a point of no importance scientifically, but of practical moment in the hands of the general practitioner, as it calls for special assistance and causes delay in the treatment of a disease where the utmost celerity is necessary. Second, the depression of the respiratory centers often to an alarming extent. And, third, the records to date, in which the character of the attack, incubation and duration periods of the disease are considered, do not show that the progress and ultimate result in any total number of cases has been modified. While magnesium sulphate will

unquestionably produce relaxation from muscular spasm and convulsion, chloretone apparently produces the same result without any of the dangers attributable to spinal injection of sulphate of magnesium.

CONCLUSIONS

Tetanus is comparatively a rare disease, occurring in temperate zones as the cause of about one in 1,520 deaths from all causes.

The mortality has not been reduced by treatment, save as to prevention.

Tetanus is five and a half to six times as frequent in the tropics as in temperate climes, owing chiefly to the variety of the disease.

In temperate zones, 86 to 87 per cent. belong to the traumatic and idiopathic variety.

In the tropics, 86 to 87 per cent. occur under 1 year of age and include tetanus neonatorum.

Climate: In temperate zones a twenty-year record shows that 68.3 per cent. occur in the warmer months of the year from May to October; 43.58 per cent. in June, July and August; most common in July and least common in March.

Tetanus predominates in the tropics; no difference worthy of note appears in the different months of the year.

Sex: In temperate zones, among males, in 4,100 cases, a ratio of 3.29 to 1, the ratio rising at various periods of life to 9.50 to 1.

In the tropics the ratio of the sexes is equal, sometimes predominating in female.

Age: Frequency at the various ages of life.

Temperate zones: 1,000 cases. Under 1 year 14.08 per cent.; 1 to 20 years, 39.80 per cent.; 20 to 40 years, 23.82 per cent.; 10 to 40 years, 50.90 per cent.

Three thousand and thirty-eight cases. Under 1 year, 22.31 per cent.; 1 to 20 years, 37.80 per cent.; 20 to 40 years, 21.09 per cent.; and 10 to 40 years, 45.32 per cent.

Tropical zones: 3,947 cases. Under 1 year, 86.47 per cent.; 1 to 20 years, 52.94 per cent.; 20 to 40 years, 34.71 per cent.; and 10 to 40 years, 51.24 per cent.

In the Canal Zone, during six years there were only twenty-five cases with twenty-one deaths and four recoveries; mortality 84 per cent. Among the cases there occurred puerperal tetanus, tetanus neonatorum, and postoperative tetanus, three of the most deadly varieties of the disease.

Leukocytosis seems to occur in tetanus, twenty-six counts averaging 13,200, not always due to the condition of the wound.

Eosinophils were diminished in six cases as in other fevers.

Incubation period, 1,092 cases, patients under 1 year excluded: One to ten days, acute tetanus, 73.35 per cent.; ten to twenty days, subacute

tetanus, 26.65 per cent. From the sixth to the ninth day, 50 per cent. of all cases are found — the maximum on the seventh day.

Duration period, 1,264 cases, patients under 1 year excluded: One to ten days acute tetanus, 78.88 per cent.; ten to twenty days subacute tetanus, 21.12 per cent.

Mortality: Other things being equal, this is very little higher in the tropics than in colder climates.

Mortality in 1,264 cases as to duration of the disease: Under one day, 90 per cent.; one to ten days, 78.32 per cent.; ten to twenty days, 25.85 per cent.; twenty to twenty-five days and over, 4.76 per cent.

Not until the tenth day does the patient have an equal chance for life and death, and between the tenth and the eleventh day the line of recovery crosses the death-line, and from this point mortality decreases steadily and rapidly regardless of treatment.

Postoperative tetanus: Incubation and duration very brief as a rule, average mortality, 86 per cent. Ninety-two cases, one to ten days, mortality 95.65 per cent.; fifty-four cases, ten to twenty-five days, mortality 76 per cent. Peritoneal interference 117 cases, mortality 90.76 per cent.; non-peritoneal, thirty-one cases, mortality 80.65 per cent.

Antitoxin is of small value save as to prevention. It should always be used in conjunction with other measures.

In estimating the value of any reported treatment as to reduction of mortality, the incubation and duration of the disease must be considered. Not until at least thirty cases can be recorded with an incubation under seven days, a duration of less than ten days, and a mortality of 55 per cent. and under, can any such treatment be accepted as modifying the prognosis. No such treatment exists at present.

I wish to express my thanks to Col. W. C. Gorgas for permission to publish this paper.

Colon Hospital.

A COMPARATIVE INVESTIGATION OF THE EFFECTS AND TOXICITY OF SODIUM SALICYLATES OF NATURAL AND SYNTHETIC ORIGIN*

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PART I.—INTRODUCTION BY TORALD SOLLMANN

There is a very prevalent, although not quite universal, belief that salicylates prepared synthetically are less effective, and especially that they are more dangerous and more toxic, than salicylates prepared from the "natural" methyl salicylate, that is, from unadulterated oil of wintergreen or oil of sweet birch. This subject is of great practical importance, on account of the extensive use of salicylic compounds in medicine, and the tendency and often the absolute need of pushing the dosage to the very limit of tolerance. If there is in fact any material difference in the effects, prescribing should certainly be confined exclusively to the less dangerous variety.

On the other hand, the difference in cost between the two varieties is very considerable. For instance one of the two synthetic brands used in this investigation is quoted, at wholesale, at 45 cents per pound, while a commercial "natural" brand costs $7.20 per pound. This difference may often be a serious consideration in itself. More serious still, however, it leads to very extensive sophistication. It is commonly stated that the adulteration begins at the still, the farmer adding the cheap synthetic methyl salicylate to his wintergreen or birch to increase the yield. Since it is difficult, if not impossible, to detect a manipulation of this kind, unless the distiller grows altogether too rapacious, even an honest manufacturer of "natural" salicylate is often not altogether certain of the purity of his product. Human nature being what it is, it may be safely assumed that some manufacturers, wholesalers and retailers are not altogether above the temptation of adding somewhat to the work which was begun by the distiller. It is therefore by no means certain that the specification "natural" always accomplishes its object — a matter which may well arouse apprehension if there is a serious difference in the action. If there is no such difference, it would be distinctly worth while to remove this apprehension and to encourage the direct prescribing of what one is more or less likely to obtain in any case.

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*The expenses of the research were in large part borne by the Therapeutic Research Fund of the American Medical Association.

*From the Pharmacological Laboratory of the Medical School of Western Reserve University, Cleveland.

From either standpoint, then, it seems important that this question of the relative toxicity of the salicylates of different origin should be definitely answered in one sense or in the other. Considering its importance, one may well be surprised at the paucity of available accurate data bearing on the question.

In the clinical literature I have not so far encountered an attempt, even — a serious, unbiased attempt — to solve the question by accurate and controlled observations. Much of the sentiment against the synthetic drug seems to be based on isolated unfortunate occurrences, such as might also occur at times with the "natural." Somehow, one is reminded of the old proverb, "Give a dog a bad name," etc. Such experiences are suggestive rather than convincing.

Experimentally, there seems to have been but one series of observations, namely that of Charteris and Maclennan. Judging from the frequency with which these observations are quoted by the advocates of "natural" salicylic acid, it is evident that they have been generally considered pertinent, valid and important.

Dr. Waddell's repetition of this work shows, however, that the results were not reliable, owing in part, at least, to the choice of animals (rabbits) which exhibit considerable differences in their susceptibility to salicylates. The experiments were not sufficiently extensive to discount this idiosyncrasy. This, of course, could not be predicted. But even granting that the observations were reliable, and thus granting the presence of dangerous impurities in some samples of synthetic salicylates, as they were on the market in 1889 when Charteris' experiments were made — granting all this, it would not follow that the synthetic salicylates marketed over twenty years later would, of necessity, be equally impure or equally dangerous.

In view of the importance and uncertainties of the question, the Research Committee of the Council on Pharmacy and Chemistry has planned a thorough-going investigation, along both clinical and experimental lines. The present paper is the first fruit of this investigation.

In planning these experiments, we had no occasion to doubt the validity of the results of Charteris. We desired, however, to ascertain whether the samples now on the market showed similar impurities, and to check and extend his observations on other species of animals. Dr. Waddell very kindly undertook to make all the experiments and observations; but they were abundantly checked by Dr. J. D. Pilcher and by myself.

The first problem concerned the securing of proper samples. For the reasons pointed out, we did not feel satisfied with accepting the commercial samples of "natural" salicylate as necessarily true to name. This difficulty was fortunately overcome by an offer of Prof. J. U. Lloyd,

of Cincinnati, to prepare for us a supply of sodium salicylate from natural oil of birch, made under his personal supervision. As a check, however, we also used a sample of sodium salicylate purchased from a firm (Merrell) which has been especially active in sounding the dangers of synthetic salicylates, and which should therefore take special pains that these do not contaminate their "natural" salt.

For the synthetic samples, we desired to secure some of the poorest specimens which are actually dispensed to patients. To this end we had a druggist place an order with two Chicago wholesale houses for "2 lbs. sodium salicylate, cheapest bulk." All of these samples are being examined chemically at the Association laboratory, and this examination will be reported in due time.

Passing now to the results, which are herewith reported by Dr. Waddell, it is evident that *there is no difference in the effects or toxicity of the samples examined, the most carefully prepared and expensive "natural," and the cheapest "synthetic."*

This raises two further questions: (1) Can these conclusions be extended to man? and (2), Can they be extended to all samples of synthetic salicylate?

1. Can the conclusions be extended to man? The extensive use which has been made of Charteris' results by the opponents of synthetic salicylates fortunately saves us the necessity of replying to the line of argument which is usually put forward when experimental evidence conflicts with commercial interests.

The cautious will always be careful in extending animal experiments to the human subject, and will keep an open mind until the clinical checks have been made. However, it may fairly be concluded that if a toxic impurity were really present in the synthetic samples, it would have manifested its dire effects in at least one of the three widely differing species of animals (cats, rats and rabbits) which were here used.

2. Can the results be extended to all samples of synthetic salicylates? To this there can only be one answer: The fact that two samples of synthetic salicylates were pure does *not* prove that all samples are pure. It does prove, however, that there is no cause for the indiscriminate condemnation of *all* synthetic salicylates, even the purest; and moreover, that the cheapest "stuff" supplied by drug-stores is not necessarily dangerous. If the cheapest brands are just as good as the "natural," it is probable that the standard "synthetic" brands are also good.

The matter is altogether too important, however, to warrant relying on mere probabilities. Certainty can be attained only by the direct examination of all, or practically all, of the brands on the market, and by the examination of individual samples to which bad effects have been charged. This is quite feasible, since a very few experiments on the

uniformly reacting rats will give data of sufficient accuracy. Dr. Waddell already has this investigation under way, and the four synthetic samples which have been examined so far, in addition to the two brands reported in this paper, fall within the ordinary limits of toxicity of the natural salicylates.

In conclusion I wish particularly to call attention to the concluding request of Dr. Waddell for samples suspected of producing untoward effects.

PART II.—EXPERIMENTAL INVESTIGATIONS

METHOD OF INVESTIGATION

The method employed in this comparison of the natural and synthetic salicylates consisted in administering the drugs to animals in definite dosage per kilogram and observing the symptoms produced by the smallest effective, lethal and intermediate doses of the one as compared with those of the other. Throughout this paper the following symbols are used to designate the preparation used in each instance: "D" Lloyd's natural; "M" Merrell's natural; "A-1" Fuller and Fuller Company, synthetic; "A-2" Robert Stevenson and Company, synthetic.

In all cases the drug was administered hypodermically, 0.9 per cent. saline being the solvent employed. For cats, a 10 per cent. solution was used; for rats, a 20 per cent.; and for rabbits, a 35 per cent. Both fractional and single dosage were tried. Every precaution was used to secure exactness of dosage. The required number of cubic centimeters, or decimals thereof, was measured with a pipette into a conical glass from which it was drawn into the syringe. After the injection had been made the syringe and the glass were washed and the water used for the purpose was injected at a different site from that used in the first instance. The needle was introduced into a fold of skin previously shorn, if the hair was long and thick, and after the injection had been made the site of entrance of the needle was compressed until there was no tendency to ooze. In most cases the point selected was the side of the abdomen, but injections were also made over the shoulders, over the popliteal space, and under the abdomen. The animals used were cats, wild rats, and tame rabbits. For the most part the injections were made in the forenoon and thereafter the animal was observed for six hours; if it survived, its condition was noted next morning.

The experiments on the different animals will now be discussed in their several groups. Under each dosage a table will be given showing the drug used, the weight of the animal, and the leading symptoms. Special features will be described in brief notes following each table.

EXPERIMENTS WITH CATS

General Description.—All the cats used were in good physical condition; they were kept during the course of the experiments in wire cages

with sawdust on the floor and were provided with bread, milk, cooked meat and water. Seventeen animals were experimented on, divided into five groups of different dosage, some of each receiving the synthetic and others the natural. The most characteristic symptoms noticed were vomiting, increase of reflexes, extreme weakness, convulsions and death. Vomiting, occurring in the case of every cat except one, was a very early symptom and was produced in from twenty minutes to one and one-half hours in 90 per cent. of the animals. Whether early or late bore no relation to the kind of salicylate or the dose given.

Origin of Salicylate Emesis.—It is interesting to note that emesis follows on hypodermic injection of salicylates, after a latent period of at least twenty minutes. Repeated examination failed to reveal the presence of salicylates in the vomitus. Salicylates may, therefore, produce emesis by a central action.

Increase in reflexes was shown without exception. It became evident in from forty minutes to two hours and forty-five minutes, and was independent of dosage or kind of salicylate. Usually the first indication was a slight tremor about the head, most evident when the animal's attention was attracted in some way. It resembled the "intentional tremor" of multiple sclerosis. Usually developing about the same time (fifty minutes to two hours forty-five minutes) the cat evinced a hypersensitiveness to sound. This, at first transient, soon became permanent and increased in acuteness until the faintest sharp noise caused the animal instantly to rise bodily from the floor. Later on (one hour seventeen minutes to five hours twenty minutes) the animal exhibited a kind of restlessness manifested by frequently getting up and lying down or turning from side to side. Coexisting with the restlessness or succeeding it, great weakness was exhibited, in that the animal if it tried to walk was unsteady and seemed to be weak in the lumbar region. Very late in the course of the experiment (one hour thirty-four minutes to five hours) it assumed a prone position with its feet and legs at its sides, which was followed in a short time by abduction of the forelegs and descent of the chin to the floor. In many instances, in from one hour thirty-five minutes to five hours, the animal rolled over on its side and lay with its feet at right angles to its body. About this time (from one hour thirty-five minutes to five hours) the animal when held by its hind legs was unable to bite the hand.

Immediately following the above, the animal went into convulsions. The onset was characteristic. The ears would suddenly be tucked down, the hair on back and tail rise up, the back arch and the head flex acutely, after which came a series of clonic convulsions involving chiefly the extremities. At the onset, the cat would partly rise on its feet and then tumble forward on its face. The limbs were the last parts to be involved and continued their rapid to-and-fro motion as the seizure wore off. Each

convulsion lasted for half a minute. In the intermission, varying from one to five minutes, the animal usually lay on its side in a relaxed condition.

After one or more convulsions the attacks would cease; respiration then became irregular, slow and finally gasping. The heart, which was irregular and very rapid before respiration ceased, became slow and regular, and continued for a few seconds. As the animal died, the sphincters were relaxed in most cases; the pupils were widely dilated and the lips blue and covered with froth. Early in the course of the experiment (from fifty minutes to two hours twenty-five minutes) dyspnea was marked; salivation was present; the animal refused to take food or water. In none of them was there any evidence of paralysis until after the convulsion; examination for this symptom was made from time to time by having the animal climb down the side of the cage. Up to the time of the convulsions, the ability to coordinate was unimpaired.

The experiments performed on cats were as follows (time of occurrence of symptoms is given in hours and minutes calculated from the beginning):

EXPERIMENT 1.—Three cats were given 1.4 gm. per kg. of salicylate in fractional dosage; i. e., 0.2 gm. per kg. every fifteen minutes.

Drug	Wt. in Kg.	Emesis	Increased Reflexes	Convulsion	Death
D	1.38	1:06	1:53	3:23	3:50
A-1	2.00	0:30	2:20	3:25	3:30
A-1	1.54	....	2:00	2:35	2:50

From the time of the injection all refused to eat or drink and soon showed evidences of salivation. During the time of observation all became very dyspneic and showed a reduction in temperature of 2° C. The symptoms were typical in each case, except that one did not vomit. During the last convulsive seizure the sphincters were relaxed and a quantity of pale urine voided. Post-mortem signs bore evidence of death by asphyxia.

There was no difference in the effects produced by the synthetic (A-1) and the natural (D).

EXPERIMENT 2.—Five kittens were given 1.2 gm. per kg. in divided doses as in Experiment 1.

Cat	Drug	Wt. in Kg.	Emesis	Increased Reflexes	Convulsion	Death
1.	D	0.70	1:09	1:20	1:35	1:55
2.	D	0.40	0:55	1:20	1:35	1:52
3.	A-1	0.70	1:05	1:17	2:28	2:30
4.	A-2	0.42	1:33	....	1:43	4:08
5.	A-2	0.50	4:18	2:45	6:15	18:00

Among these the first three are practically like one another and those of Experiment 1; there were dyspnea, salivation and a reduction of temperature of half a degree C. in each case. The fourth compared favorably with the first three, except that there was no marked dyspnea and no increase in reflexes[1] (auditory). The fifth showed delayed occurrence of all the symptoms.

Here, then, again as in Experiment 1, the synthetic and the natural show no essential differences. What difference there is in time of death is in favor of the synthetics, especially A-2.

1. Whether this animal was deaf had not been determined.

Since death does not occur for several hours, the fractional dose method seemed unsuitable for determining the just-fatal dose, and the entire quantity was therefore administered in a single injection in the following experiments.

EXPERIMENT 3.—Two cats were given 1.1 gm. per kg. in one injection.

Drug	Wt. in Kg.	Emesis	Increased Reflexes	Convulsion	Death
D	1.26	0.50	1.30	5.00	5.30
A-1	1.26	0.60	0.50	2.15	2.35

Here, with two animals of exactly the same weight and receiving the same dosage, one of the synthetic, the other of the natural, the symptoms were different, only in the time of occurrence, in favor of the natural. Dyspnea was very marked and was exhibited late. The convulsions seemed more severe than in Experiments 1 and 2. There was no relaxation of the sphincters at death.

EXPERIMENT 4.—Four cats were given 1.0 gm. per kg. as in Experiment 3.

Cat	Drug	Wt. in Kg.	Emesis	Increased Reflexes	Convulsion	Death
1.	D	0.48	0:45	1:40	0 in 6:00	18:00
2.	D	0.51	0:60	2:15	5:11	18:00
3.	A-1	0.40	3:30	1:40	0 in 6:00	18:00
4.	A-2	0.90	0:15	1:15	3:45	18:00

The third did not vomit until late; Nos. 1, 3 and 4 did not show much dyspnea and Nos. 1 and 3 did not have convulsions within 6 hours, but by this time Nos. 1 and 4 were too weak to stand, while No. 3 was in very good condition. All died during the night.

In this experiment the results differ chiefly in the failure of two of the animals to have convulsions within six hours and delayed emesis in the case of the synthetic (A-1).

EXPERIMENT 5.—Three cats were given less than 1.0 gm. per kg.

Cat	Drug	Wt. in Kg.	Dose	Emesis	Increased Reflexes	Convulsion	Death
1.	D	1.60	0.8	:20	1:00	0 in 6:00	24:00
2.	A-1	2.70	0.9	:55	1:10	5:35	6:00
3.	A-2	2.30	0.9	:45	1:15	0 in 6:00	24:00

Cats 2 and 3 showed marked dyspnea; Cats 1 and 3 did not have convulsions within the time of observation, and on the morning following were very weak, refused to eat, and evinced increased reflexes; both died during the day.

The slight differences in this experiment are in favor of the synthetic (A-2) (delayed vomiting and delayed death).

These five series of experiments show that the synthetic and the natural salicylates affect cats essentially alike. Taking all the experiments as a whole and comparing them symptom by symptom, we find them just about the same in kind and in time. For instance, vomiting (with one exception, and that in favor of the synthetic) occurred early as often with one as with the other. The reflex disturbances did not differ in kind and were as often early in one as in the other, while the one failure to occur was after the synthetic (A-2). The data are also equally divided as regards fatality, for out of five receiving the natural,

four had convulsions and died within six hours, while one died in eighteen hours, and out of the same number receiving the synthetic the same effects were observed. Therefore, considering the results as a whole, no essential differences were observed in the effects produced in cats, whether the natural or the synthetic was used.

These results tabulated in percentages are as follows:

Dose per Kg.	Emesis	Increased Reflexes	Weakness	Convulsion	Death
1.4-1.0	90[1]	90[2]	50[3]	100	100
1.0-0.8	100	100	58[4]	42[5]	100

1. The failures were with A-1.
2. The failures were with A-2.
3. Failures equally divided between the natural and the synthetic.
4. The failures were with the natural (D).
5. Exhibited as often after the natural as after the synthetic.

EXPERIMENTS WITH WILD RATS

General Description.—The rats used in these experiments were common wild rats, caught with cage-traps in neighboring stores and stables. All the rats used were uninjured and in good condition and were kept in wire cages, provided with bread, cheese and water. In most cases they were used on the day of their capture. They were weighed in a small box into which they were allowed to "escape" for the purpose. In making the injection a portion of skin was drawn through the meshes of the cage with long forceps, so that on the whole the animal was disturbed very little. Thirty-six of these animals were used, being divided into seven groups receiving different dosage, some the synthetic, others the natural. The most striking symptoms noticed were increase of reflexes, stupor, salivation, convulsions and death. However, only the last two were what may be called characteristic; the others being of variable occurrence.

The increase in reflexes, when evinced, resembled the same symptom in cats. It occurred in about 50 per cent. of those which had received fatal doses. During the course of the experiment most of them became very dyspneic, and showed evidences of salivation. A sort of stupor was exhibited later; i. e., they appeared dazed and if poked would not try to bite. But even this was no more constant than increase of reflexes. Unlike the cats, they would drink at times. Many assumed a prone position for a short time just prior to the convulsion. Then they would suddenly spring up from the floor and fall over on the side in a convulsion. In most cases the convulsions lasted for half a minute and were repeated at intervals of one minute, in some instances as often as ten times. The convulsion resembled that in the cat. At the onset there was emprosthotonos, which continued throughout each attack, while a violent, rapid to-and-fro motion engaged the head and the limbs. The

convulsions gradually subsided and the animal remained lying weakly on its belly.

The phenomena of death were the same as in the cat. The sphincters were usually relaxed; the lips were blue and covered with froth.

EXPERIMENT 1.—Two rats were to receive 2 gm. per kg. in fractional dosage; i. e., 1 gm. per kg., in half an hour 0.2, and thereafter 0.2 gm. every quarter hour.

Rat	Drug	Wt. in Kg.	Increased Reflexes	Convulsion	Death
1.	D	0.26	....	....	1:00
2.	A-1	0.38	1:00	2:05	2:06

The first rat drank once, became very dyspneic and died after receiving 1.6 gm. per kg., without convulsion or other symptom. The second lived for twenty minutes after the last injection and showed a characteristic chain of symptoms. After the third injection it drank freely; after the fourth (one hour) it became very irritable to sound and evinced tremor at intervals. These symptoms increased in intensity toward the end, which occurred during the first convulsion. The natural in this case proved to be the more toxic.

EXPERIMENT 2.—Four rats were given 2 gm. per kg. at one injection.

Rat	Drug	Wt. in Kg.	Increased Reflexes	Convulsion	Death
1.	D	0.062	....	0:11	0:12
2.	D	0.061	....	....	0:17
3.	A-1	0.064	....	....	0:17
4.	A-1	0.067	0:20	0:21	0:28

The fourth alone showed increased reflexes; otherwise Rats 1 and 4 were alike. In this experiment with animals of the same size, there was a singular pairing of effects, giving about the same results for the synthetic as for the natural.

EXPERIMENT 3.—Two rats were given 1 gm. per kg. as in Experiment 2.

Rat	Drug	Wt. in Kg.	Increased Reflexes	Convulsion	Death
1.	D	0.36	0:55	1:10	1:13
2.	A-1	0.38	1:05	1:25	1:28

The first evinced tremor; Rat 2 urinated during the time of observation; both were very irritable to sound and compared closely all through, except in the slight difference in the time of occurrence of the symptoms, in favor of the synthetic. Neither relaxed the sphincters at death and at autopsy their bladders were empty.

EXPERIMENT 4.—Six rats were given 0.75 gm. per kg. at one injection.

Rat	Drug	Wt. in Kg.	Increased Reflexes	Convulsion	Death
1.	D	0.180	....	1:03	1:08
2.	D	0.240	....	0:36	0:37
3.	M	0.160	....	0:38	0:43
4.	A-1	0.063	1:13	1:33	1:43
5.	A-1	0.120	....	1:29	1:29
6.	A-2	0.110	....	0:35	0:35

The fourth alone showed unmistakable increase in reflexes; otherwise all behaved alike, showing dyspnea, salivation, stupor, and finally convulsions followed by death without relaxation of sphincters. There was some difference in the time of occurrence of the symptoms, but this was not greater in the case of a difference in drug than in case of the same drug on a different animal.

EXPERIMENT 5.—Eight rats were given 0.65 gm. per kg.

Rat	Drug	Wt. in Kg.	Convulsion	Death
1.	D	0.170	0:18	0:25
2.	M	0.065	0:35	1:37
3.	M	0.140	....	....
4.	M	0.070	0:56	1:06
5.	A-1	0.115	0:40	0:50
6.	A-2	0.110	0:32	0:45
7.	A-2	0.150	0:50	1:00
8.	A-2	0.120	0:53	1:05

One of those receiving the natural (M) exhibited no symptoms, while all the other animals with this and with the three other preparations had convulsions and died. Increased reflexes occurred in Rat 4, which had received the injection of the natural (M).

EXPERIMENT 6.—Five rats were given 0.50 gm. per kg. at one injection.

Rat	Drug	Wt. in Kg.	Convulsion	Death
1.	D	0.180	....	....
2.	M	0.140	0:33	0:55
3.	A-1	0.063	....	....
4.	A-1	0.037	....	....
5.	A-2	0.031	....	....

The second alone had convulsions and died. It may be noted that this was the same preparation of the natural that had proved an exception in the opposite direction, in Experiment 5.

EXPERIMENT 7.—Eight rats, ranging in weight from 0.052 kg. to 0.200 kg. were each given 0.35 gm. per kg. at one injection (two rats for each sample, D, M, A-1 and A-2). None of them showed any symptoms.

In the case of the rats, it has been shown in the above experiments that the symptoms following the administration of the synthetic and the natural are almost identical. Profound disturbance was manifested as often with one as with the other. The following percentage table will show this more clearly:

All Preparations in Doses of gm. per Kg.	Increased Reflexes, Per cent.	Stupor, Per cent.	Convulsion, Per cent.	Death, Per cent.
0.75-2.00	50.0	60	80*	100.0
0.65	12.5	..	75†	87.5‡
0.50	..	..	16§	16§
0.35	..	..	..	....

* The failures to exhibit this symptom occurred with the natural D (14 per cent.) and synthetic A-1 (6 per cent).

†The failures in this case occurred with the natural M and the synthetic A-2 (each 12.5 per cent.).

‡Only one failure and it occurred after natural M.

§Occurred only after natural M.

EXPERIMENTS ON RABBITS

The rabbits used were tame ones secured from a local dealer. They were kept in wire cages having sawdust spread on the floor, and were fed on bread and cabbage and given free access to water. When large injec-

tions were made the point where the needle entered was ligated to prevent oozing. Twenty-seven experiments were performed on these animals, divided into six groups receiving different dosage, some the natural, others the synthetic.

The most striking symptoms were extreme weakness, convulsions and death. As a rule the animal showed few symptoms. The earliest effect was a loss of appetite; and if profoundly affected, the animal ceased to be playful or to take notice, having a tendency to stay by itself. In only a few cases was there an evident increase in reflexes as evinced by tremor and sensitiveness to sound. Most of the animals drank at intervals, became salivated, and urinated during the course of the experiment. Just prior to the convulsion the rabbit would assume a prone attitude like that described in the cat. Gradually its chin sank to the floor, following which there was a falling, of the head first and then of the body, to one side. The animal lay in this position for a few minutes with feet at right angles to the body and head acutely flexed. When the convulsive seizure came, its head would become sharply extended, while the spine remained slightly arched and its limbs underwent the same to-and-fro movements observed in cats and rats. The convulsion was in most cases repeated at intervals of from one to five minutes; during the intermission the animal lay weakly on its side or belly. As death approached, the attacks became weaker and weaker, and the respiration slow, irregular, and finally gasping. The heart continued for a few beats, being very slow but regular. As a rule the sphincters were relaxed. Post-mortem examination showed evidence of asphyxiation.

Preceding my data under each dosage I will give briefly the results obtained by Charteris and Maclennan[2] wherever the dosage is the same. They administered, in one of their experiments, 5.22 gm. per kg. of natural sodium salicylate with only transient effects, the animal recovering perfectly in four hours. I did not repeat this experiment, since much smaller doses proved fatal in my rabbits.

EXPERIMENT 1.—Charteris and Maclennan, experimenting on rabbits, found 2.93 gm. per kg. of the synthetic salicylate fatal, while the same dose of the natural caused only transient disturbances. They used a solution in distilled water (2 gr. in 6 minims) and administered it hypodermically, in fractional dosage, as follows: The first four injections, at intervals, respectively, of six minutes, thirty minutes, and thirty minutes, were each of 12 minims (or 4 gr., equivalent to 0.65 gm. per kg.) and the fifth, at an interval of four minutes from the fourth, was of 6 minims (or 2 gr., equivalent to 0.33 gm. per kg.).

In the course of my investigations, I repeated their procedure on one rabbit using Lloyd's natural salicylate (D). Since my results differed greatly from theirs, I will give their observations in comparison with mine. The total dosage at any time in the experiments is enclosed in brackets.

I. Charteris and Maclennan; natural salicylate; one rabbit, weighing 0.397 kg.

2. Charteris and Maclennan: Brit. Med. Jour., 1889, ii, 1208.

The first effect noted was a transient spastic condition of the hind legs, which followed the second injection (1.30 gm. per kg.). The second effect noted was paresis of the hind legs and tremor, which followed the third injection (1.95 gm. per kg.). The third effect noted was a transient increase of the paresis and tremor, which followed the fourth injection (2.61 gm. per kg.). No further symptoms were noted and recovery was perfect. Total drug used was 18 gr., equivalent to 2.93 gm. per kg.

II. Charteris and Maclennan; synthetic salicylate; one rabbit, weighing 0.397 kg.

Immediately after the first injection (0.65 gm. per kg.) there were backward movements and transient paralysis of the flexors of the hind legs. Immediately after the second injection (1.3 gm. per kg.) there were rapid backward and circular movements with paresis and dragging of the hind legs. After the fourth (2.61 gm. per kg.) the paralysis was more pronounced and protracted; prostration was more marked; and the reduction in temperature was 0.4° F. Following the fifth injection (2.93 gm. per kg.) a "new symptom" was noticed. There was a distinct paralytic condition of the fore legs, the animal having no control of them; they would slip under when it tried to walk forward so that the breast and the jaw rested on the table. Paralysis deepened, and became more general until the animal seemed to lose control of all muscular movement. Just before death occurred, the paralysis of the fore legs seemed to be more marked than that of the hind legs, which seemed to have recovered. The animal died in an hour and thirty minutes from the beginning of the experiment. Total drug used was 18 gr., equivalent to 2.93 gm. per kg.

III. Performed in this laboratory; Lloyd's natural salicylate (D); one rabbit, weighing 0.720 kg.

After the first injection (0.65 gm. per kg.) the animal squealed several times and ran around the cage a few turns, but seemed normal. After the second injection (1.3 gm. per kg.), it ate a little bread and seemed to be perfectly normal. After the third injection (1.95 gm. per kg.) there was evidence of dyspnea, the respiratory rate being 120; the temperature had now fallen 2° F. After the fourth injection (2.61 gm. per kg.) the dyspnea was more marked, the respiratory rate being 150. No further symptoms were noticed until twenty minutes after the last injection, when the animal began to exhibit restlessness and seemed to prefer to lie flat on its belly; it could, however, walk and sit in a normal manner; there was no paralysis. After thirty more minutes had elapsed, the animal exhibited more marked restlessness; tremor and irritability to sound were evinced; following the development of these symptoms, the animal assumed a prone attitude with its chin on the floor between its fore legs; there was no paralysis. Five minutes later there was a convulsion, which was repeated in five minutes. After the second convulsion, the rabbit lay on its side in a relaxed condition, and the respiration became slow and labored. It died from asphyxia in five minutes after the second convulsion, its pupils being widely dilated and its sphincter relaxed. The animal died in two hours sixteen minutes from the beginning of the experiment. Total drug used was 2.93 gm. per kg.

To summarize: At the same dosage per kg. both the natural and the synthetic used by Charteris and Maclennan were more paralytic than the natural used in this laboratory; their natural, less fatal; and their synthetic equally fatal, but less convulsive.

EXPERIMENT 2.—Charteris and Maclennan administered 1.14 gm. per kg. of the synthetic salicylate to a rabbit in divided doses (0.163 gm. per kg. at five-minute intervals). They observed after the fourth injection (0.652 gm.), excitement, backward and circular or rotatory movements; then transient paralysis of the flexors of the hind legs so that a forward movement was performed by dragging on the belly. These lasted about one minute. No further symptoms developed and the animal recovered.

As a comparative experiment they administered to another rabbit 1.0 gm. per kg. of the natural in the same manner, and no symptoms developed.

In this laboratory, eight rabbits were experimented on with the dosage and mode of administration quoted above. The preparations of salicylate used and the results are as follows:

Rabbit	Drug	Wt. in Kg.	Increased Reflexes	Convulsion	Death
1.	D	0.60	....	none observed	18:00
2.	D	1.20	....	....	lived
3.	M	1.40	....	....	lived
4.	M	0.82	....	....	lived
5.	A-1	0.45	2:30	2:48	2:50
6.	A-1	0.70	....	0:53	1:40
7.	A-1	1.40	....	....	1:37
8.	A-2	0.34	0:45	3:20	4:20

The four which were given the synthetic died within six hours, while only one having the natural died and this not until after six hours. Of the acutely fatal, one (7) showed no symptoms, but the symptoms exhibited by the other three resembled those of rabbit D of Experiment 1. Salivation was evident in No. 8. The one which died late, though weak and dyspneic, did not have a convulsion within six hours. All which survived showed no symptoms except dyspnea and loss of appetite, and they were playful and hungry inside six hours. It may be noted that those which received the synthetic fared worse than the others.

To summarize: The results on eight rabbits appear decidedly unfavorable to my synthetic as compared with my natural salicylates; but further, both my synthetics (A-1 and A-2) and my natural salicylate (D) appear to be more fatal than the synthetic used by Charteris and Maclennan.

EXPERIMENT 3.—Charteris and Maclennan did not find either the natural or the synthetic fatal when given fractionally to the extent of 1.55 gm. per kg. and observed just about the same symptoms quoted in Experiment 2. My data with a dosage of 1.4 gm. per kg. at one injection are as follows:

Rabbit	Drug	Wt. in Kg.	Convulsion	Death
1.	M	0.860	5:34	6:00
2.	A-1	1.140	....	lived
3.	A-1	1.040	....	lived
4.	A-1	1.700	....	lived

Except loss of appetite, none but the one that died showed any symptoms.

In this experiment the natural (M) fared worse than the synthetic (A-1) and worse also than Charteris and Maclennan's natural and synthetic.

EXPERIMENT 4.—Seven rabbits were given 1.2 gm. per kg. at one injection.

Rabbit	Drug	Wt. in Kg.	Increased Reflexes	Convulsion	Death
1.	D	0.80	....	1:50	2:10
2.	D	0.80	....	2:40	3:10
3.	M	0.98	....	....	lived
4.	A-1	0.88	....	....	lived
5.	A-1	1.12	2:30	....	lived
6.	A-1	1.26	1:10	....	lived
7.	A-2	1.34	3:55	4:00	4:02

All became dyspneic and refused to eat. There was a reduction in temperature of about 2° C. in each case. Only the last three showed an increase of reflexes. At the end of the experiment those that survived seemed normal. It is very striking that all that had received an injection of D, a natural salicylate, died, while all receiving A-1, synthetic, lived; also that one rabbit survived after M, natural, and one died after A-2, synthetic.

The results, therefore, are in favor of the synthetic.

EXPERIMENT 5.—Charteris and Maclennan did not find 1 gm. per kg. of the natural productive of any symptoms in the one experiment they performed. Administering 1 gm. per kg. at one injection I obtained the following results:

Rabbit	Drug	Wt. in Kg.	Effects	
1.	D	0.92	No symptoms	lived
2.	D	1.20	No symptoms	died in 18 hours
3.	A-1.....	1.00	No symptoms	lived
4.	A-2.....	0.90	No symptoms	lived

None of these exhibited any characteristic symptoms. They urinated profusely, refused to eat, and lay huddled together for the first few hours; after that they became playful and hungry. One, however, that had received the natural died during the night.

Those with the synthetic, therefore, fared better.

EXPERIMENT 6.—Three rabbits that had resisted smaller doses were given 1.6 gm. per kg. at one injection.

Rabbit	Drug	Previous Drug	Wt. in Kg.	Convulsion	Death
1.	D	A-1, 1.4	0.96	5:30	6:00
2.	A-1	A-1, 1.2	0.84	0 in 6:00	18:00
3.	A-2	A-1, 1.4	1.20	2:35	2:40

The second, though failing to have convulsions or die during the term of the observation, was dyspneic, irritable and weak, and maintained a prone attitude.

Taking the experiments as a whole, it is seen that the natural and the synthetic salicylates affected rabbits essentially alike, the failures in one experiment being practically offset in another. Presented in tabular form we find the results as follows:

Dose gm. per kg.	Increased Reflexes Per cent.	Convulsion Per cent.	Death Per cent. .....
1.6	33*	66†	100
1.14	62	40	62‡
1.4-1.2	40	40	40§

*Was shown in case of the synthetic.

†Present as often with the natural as with the synthetic.

‡In fractional dosage more constant with the synthetic, but in single dosage with the natural.

§More constant after natural (D).

COMPARISON WITH THE RESULTS OF CHARTERIS AND MACLENNAN

Comparing the results of Charteris and Maclennan with those obtained by me, there are seen to be very great differences, which are difficult to explain:

As regards fatality Charteris and Maclennan had no fatality with the natural, even with a dose as high as 5.22 gm. per kg. Our natural salicylate showed a 100 per cent. fatality with doses between 1.4 and 2.93 gm. per kg.; and a 44 per cent. fatality with doses between 1.0 and 1.2 gm. per kg. Our natural salicylate appears, therefore, to be much more toxic than that of Charteris and Maclennan.

With their synthetic, Charteris and Maclennan found 2.93 gm. fatal, 1.6 not fatal. Our synthetic showed a 100 per cent. fatality even with 1.6 gm. and a 38.5 per cent. fatality between 1 and 1.4 gm. Our syn-

thetic, therefore, also appears to be more toxic than theirs; but whereas they claim a great difference in the relative toxicity of their natural and synthetic samples, ours are essentially alike; indeed the synthetic are mathematically somewhat *less* toxic; but the difference falls well within the limits of error.

In this connection, I would point out that Charteris and Maclennan used only one animal for each dosage. Indeed, to judge from their comments, it appears that they used only two animals in their investigation, one for all the doses of the natural, and the other for all the doses of the synthetic. If so, they neglected the ordinary precaution of excluding idiosyncrasy by control tests. Our results show that this is very necessary for rabbits, for these animals exhibit considerable individual variation: some animals survived as high as 1.4 gm. per kg. while others died with 1 gm. and several with 1.14 gm. This individual resistance is quite limited, however, for, as shown in my Experiment 6, three rabbits which had survived from 1.2 to 1.4 gm., all died with 1.6 gm. Our results, therefore, cannot explain the survival of the rabbits from the large doses employed by Charteris and Maclennan. They might possibly be due to differences of food, but it would be idle to speculate on the basis of the scanty data which are furnished.

The size of the animal did not seem to be a factor in any of my experiments; certainly not among the cats and the rats, and it is not evident among the rabbits, since large ones died as often and as soon from small doses as did the small ones from large doses; and with the same dosage results were about equally divided.

There was a seeming difference in resistance on the part of certain rabbits; out of four injected with 1.0 gm. per kg. only the largest died: out of seven with 1.2, the two smallest and the largest died; of three with 1.6 gm. per kg., all fatal, the two largest died several hours sooner than the smallest.

Another marked difference in our results is in the description of the symptoms. Charteris and Maclennan describe an immediate reaction, consisting in excitement, rotatory movements and transient partial paralysis, occurring in both rabbits with non-fatal doses, but much more marked and with much smaller doses in the synthetic. None of my rabbits exhibited anything resembling this description even remotely. This suggests that the symptoms were a peculiarity of the particular animals — and this in turn would explain why they were so slight in the "natural" rabbit. The immediate occurrence and transient character of the symptoms suggest that they were due to local irritation rather than to the systemic action of the salicylate.

The true salicylate symptoms shown by my animals did not occur until later and only with doses which approximated the fatal.

PART III.—SUMMARY OF EFFECTIVE AND FATAL DOSES

In the following, an attempt is made to place the relations of dosage, effects, and rapidity of action on a quantitative basis. For the sake of simplicity, the four samples are here grouped together. This is justified by the close agreement in their effects, which have been described with sufficient detail in Part II of this paper. For the fatal dosage, however, the natural and synthetic are also tabulated separately.

Except loss of appetite and salivation, which were present in all the animals experimented on, early symptoms were constantly present and unmistakable only in the case of the cats.

Anorexia was present in all cats, almost from the moment of injection, no matter how small the dose; even after 0.2 gm. per kg. in the course of the experiments with fractional dosage; and in the animals that did not die acutely it persisted. This applies not only to food but also to water; I have seen the animals repeatedly approach the vessel containing water and touch the surface with the nose, but turn away without drinking a drop.

Emesis occurred in 94 per cent. of all cats and is tabulated as follows:

Time in Hours	Number of Animals	Per cent. of Animals	— Dose Administered when Emesis Occurred — 1.4	1.2	1.1	1.0	0.9	0.8	0.6
			Number of Animals						
¼- ½	3	17	1	..	..	1	..	1	..
½- ¾	2	12	..	..	..	1	..	..	1
¾-1	3	35	..	..	1	1	2	2	..
1 -1¼	2	12	..	.	1	1	..	..	..
1½-2	2	12	..	1	..	1	..	..	..
4¼	1	6	..	1	..	..	..	..	..
Failed	1	6	1	..	..	..	..	..	..

Examination of this table will show (1) that 0.6 gm. per kg. may produce vomiting; (2) that the largest ineffective dose was 1.4 gm. per kg.; (3) that the shortest time was fifteen minutes; (4) that the longest was four hours fifteen minutes; (5) half of the animals vomited within three or four hours and two-thirds within an hour (a delay of over two hours is exceptional); (6) that the time of the vomiting is not dependent on the dosage, large doses not hastening and small not delaying the effect; (7) that emesis occurred just as readily after natural as after synthetic (of seven cats receiving between 0.8 and 1.1 gm. all vomited; of ten cats receiving 0.6 to 1.4 gm. of synthetic, all but one vomited — this had received 1.4 gm.).

Increased reflexes were present in 94 per cent. of all cats and are tabulated as follows:

Time	Number of Animals	Percentage of Animals	Effective Dose in gm. per kg. 1.4	1.2	1.1	1.0	0.9	0.8
			Number of Animals					
0:50-1:20	8	47	..	3	1	1	2	1
1:21-1:50	3	17	..	..	1	2	..	..
1:51-2:20	4	24	3	..	..	1	..	..
2:20-2:45	1	6	..	1	..	..	..	..
Failed	1	6	..	1	..	..	..	..

This table shows (1) that increased reflexes may occur with 0.8 gm., but (2) may be absent with 1.2 gm. per kg.; (3) that the shortest time was fifty minutes; (4) that the longest was 2:45; (5) that half of the animals show the effect within 1:20; (6) that the symptom was not dependent for its occurrence or time of occurrence on the dosage.

No attempt will be made to tabulate the early symptoms in rats and rabbits. Failure to eat, but not to drink, was always present in these animals from the very inception of the drug, and at a variable later time salivation was also evident. In non-fatal cases, this and the anorexia both disappeared within six hours.

Convulsions in their relation to time of occurrence and dosage will now be considered:

Cats: Convulsions occurred in 76.5 per cent. of all the cats and are tabulated as follows:

Time	Number of Animals	Percentage of Animals	Effective Dose in gm. per kg. 1.4	1.2	1.1	1.0	0.9	0.8
			Number of Animals					
1:35-2:35	6	35	1	4	1	..	..	..
2:36-3:35	2	12	2	..	..	..	..	..
3:36-4:35	1	6	..	..	..	1	..	..
4:36-6:00	4	23½	..	1	1	1	1	..
Failed	4	23½	..	..	..	2	1	1

This table shows that (1) the smallest dose causing convulsion was 0.9 gm. per kg.; (2) the largest dose failing to cause convulsion was 1.0 gm. per kg.; (3) large doses were effective sooner than small; (4) large doses were more certainly effective; (5) shortest time was 1:35; and the longest 6:00 or later.

Rats: Convulsions occurred in 43 per cent. of all rats receiving doses of 0.5 gm. per kg. and higher; and never with 0.35 gm. per kg. The results are tabulated as follows:

Time	Number of Animals	Percentage of Animals	2.0	Effective Dose in gm. per kg. 1.6	1.0	0.75	0.65	0.50	0.35
				Number of Animals					
0:11-0:41	12	43	2	..	..	3	6	1	..
0:42-1:11	2	7	..	..	1	1	..	..	..
1:12-1:41	3	11	..	..	1	2	..	..	..
1:42-2:05	1	3	1	..	..	..	..	..	..
Failed	10	36	2	1	..	..	2	5	8

This table shows (1) that the smallest dose causing a convulsion was 0.50 gm. per kg.; (2) that the largest failing, 2.0 gm. per kg.; (3) that increasing the dose increases the liability to die without convulsion; (4) that doses below 0.65 gm. per kg. are rarely convulsive; (5) that 1.0 gm. per kg. to 0.75 gm. per kg. produces convulsions in 100 per cent.

Rabbits: In the rabbits convulsions occurred in 37 per cent. with a dosage between 2.93 gm. per kg. and 1.0 gm. per kg.; 15 per cent. within the same range of dosage died without convulsions. The results are tabulated as follows:

Time	Number of Animals	Percentage of Animals	Effective Dose in gm. per kg. 2.93	1.6	1.4	1.2	1.14	1.0
			Number of Animals					
0:53-1:53	2	8	..	..	..	1	1	..
1:54-2:54	4	15	1	1	..	1	1	..
2:55-3:55	1	4	..	..	..	..	1	..
3:55-5:35	3	11	..	1	1	1	..	..
Failed	17	63	..	1	3	4	5	4

This table shows that (1) the smallest dose causing a convulsion was 1.14 gm. per kg.; (2) the largest failing 1.6 gm. per kg.; (3) between these limits 38 per cent. had convulsions with dosage of 1.2 gm. per kg. and 25 per cent. with dosage of 1.4.

As was previously pointed out, the convulsant effects were alike for the four samples.

Death.—Cats: These proved to be very susceptible to the salicylates; the mortality was 100 per cent. with a dosage of 1.4 to 0.8 gm. per kg. The results are tabulated as follows:

Time	Number of Animals	Percentage of Animals	Effective Dose in gm. per kg. 1.4	1.2	1.1	1.0	0.9-0.8
			Number of Animals				
1:52-2:52	5	30	1	3	1	..	..
2:53-3:52	2	12	2	..	..	..	..
3:53-4:52	1	6	..	1	..	..	..
4:53-6:00	2	11	..	..	1	..	1
6:00-18:00	5	29	..	1	..	4	..
18:00-24:00	2	12	..	..	..	..	2
Total fatal	17	100	3	5	2	4	3

This table shows (1) that the smallest fatal dose was 0.8 gm. per kg.; (2) all doses above 0.8 gm. per kg. were fatal; (3) increase in dosage hastens death; (4) the shortest time in which death occurred was 1:52.

Rats: These proved to be very suitable animals, giving uniform results. The deaths are tabulated as follows:

Time	Number of Animals	Percentage of Animals	Effective Dose in gm. per kg. 2.0	1.6	1.0	0.75	0.65	0.50	0.35
			Number of Animals						
0:12-0:42	7	19	4	..	..	2	1	..	..
0:43-1:12	9	25	..	1	..	2	5	1	..
1:13-1:42	4	11	..	..	2	1	1	..	..
1:43-2:05	2	6	1	..	..	1	..	..	..
Total fatal	22	61	5	1	2	6	7	1	..
Total lived	14	39	..	..	..	..	1	5	8

This table shows (1) that the smallest fatal dose was 0.5 gm. per kg.; (2) that the largest non-fatal dose was 0.65 gm. per kg.; (3) that the smallest 100 per cent. fatal dose was 0.75.

Rabbits: As previously stated these gave the most inconstant results obtained from any of the animals. Tabulated, the fatalities are as follows:

Time	Number of Animals	Percentage of Animals	Effective Dose in gm. per kg.[1] 2.93	1.6	1.4	1.2	1.14	1.0
			Number of Animals					
1.04-2:04	3	11	..	..	..	1	2	..
2:05-3:04	3	11	1	1	..	..	1	..
3:05-4:04	2	7	..	..	..	2	..	..
4:05-6:00	3	11	..	1	1	..	1	..
6:00-18:00	3	11	..	1	..	..	1	1
Total fatal	14	51	1	3	1	3	5	1
Total lived	13	49	..	..	3	4	3	3

1. The dose of 1.14 was administered fractionally.

This table shows that (1) the smallest fatal dose was 1.0 gm. per kg.; (2) the largest non-fatal was 1.4 gm. per kg.; (3) there is no increase of fatality corresponding to increase in dosage inside of the range of 1.0 to 1.4 gm.

COMPARATIVE FATALITY OF THE FOUR SAMPLES

This is shown in the following table, in which the denominator shows the number of animals injected, and the numerator, the number which died from this dosage. Doses which give a mortality of 100 per cent., and over, are not included since they were alike for all samples. This also excludes cats, for which the whole range of doses was uniformly fatal. The last column is particularly significant as giving a numerical expression to the relation of the different samples. As previously stated this difference is apparently in favor of the synthetic, but falls well within the limits of normal variation.

	Rats			Rabbits				Rats 0.5-0.6 and
Samples	0.65	0.5	0.6-0.5	1.4.	1.2-1.14	1.0	1.4-1.0	Rabbits 1.0-1.4
Natural D	1/1	0/2	1/3=33%	...	3/4	1/2	4/6 =67%	5/9 =56%
Natural M	2/3	1/1	3/4=75%	1/1	0/3	...	1/4 =25%	4/8 =50%
Both Natural	3/4	1/3	4/7=57%	1/1	3/7	1/2	5/10=50%	8/17=53%
Synthetic A-1	1/1	0/2	1/3=33%	0/3	3/6	0/1	3/10=33%	4/13=31%
Synthetic A-2	3/3	0/2	3/5=60%	...	2/2	0/1	2/3 =67%	5/8 =63%
Both Synthetic	4/4	0/4	4/8=50%	0/3	5/8	0/2	5/13=38%	9/21=43%
All Samples	7/8= 88%	1/7= 14%	8/15= 53%	1/4= 25%	8/15= 53%	1/4= 25%	10/23= 43½%	18/38= 47%

PART IV.—SODIUM PARACRESOTINATE

Twenty years ago Dunstan[3] isolated the ortho- and paracreosotic acids from samples of synthetic salicylic acid. Among recent writers Kunkel[4] states that the cresotic acids are of importance because they may occur as impurities in commercial salicylic acid, and Cushny,[5] that they are found in commercial samples of salicylic acid.

3. Dunstan: Brit. Med. Jour., 1891, i, 695.
4. Kunkel: Toxikologie, p. 557.
5. Cushny: Pharmacology and Therapeutics, 1910, p. 472.

Concerning the toxicity of these acids Charteris found both the orthocresotic acid and the paracresotic acid markedly toxic to rabbits when administered hypodermically in rectified spirits; 0.34 gm. per kg. of the para- acid producing convulsion in two and one-half hours and death in three hours, and the ortho- acid being fatal in even smaller doses. Kunkel[4] and Cushny[5] state that the ortho- acid affects the heart unfavorably and that the meta- acid is inactive, while the former writer says that the para- acid may be used therapeutically with good results, 6 gm. administered internally causing only dilatation of the capillaries and sweat. Kobert[6] states that the cresotic acids are qualitatively like the salicylic acids. None of these writers mentions the toxic dose of any of the cresotic acids.

Charteris, experimenting with rabbits, found that a mixture of ortho- or paracreosotic acid with natural salicylic acid greatly enhanced the toxicity of the latter.

In regard to the toxicity of the sodium salts of the cresotic acids, Cushny says that the sodium paracresotinate has been used internally and is somewhat less toxic than salicylic acid. I have not found any reference to the toxicity of the orthocresotinate.

I made a few experiments on rats and rabbits with the paracresotinate of sodium. The paracresotinate (Merck) was used because it was the only salt of cresotic acid which I could obtain at the time of the experiment. It was administered hypodermically in 10 per cent. solution in distilled water.

EXPERIMENTS ON RATS

EXPERIMENT 1.—Four rats were injected hypodermically with 0.5 gm. per kg. with the following results:

Rat	Wt. in Kg.	Convulsion	Death
1.	0.320	....	0:28
2.	0.140	....	1:50
3.	0.045	1:15	lived
4.	0.050	....	lived

All of them exhibited marked dyspnea, salivation and stupor; only one had convulsions and it recovered in fifteen minutes. Those that died, just prior to death, lay on their bellies and could not be aroused by blowing on their heads or poking objects at them. They were not paralyzed, for they voluntarily crawled at times along the floor of the cage. There was no struggle at death.

EXPERIMENT 2.—Four rats were injected with 0.45 gm. per kg.

Rat	Dose	
1.	0.343	On belly all day; recovered.
2.	0.065	On belly all day; recovered.
3.	0.191	Convulsion in 1 hour; death in 1:15.
4.	0.141	Convulsion in 1 hour; death in 1:10.

Among these the same rate of fatality occurred as in Experiment 1. The convulsive effect was greater.

EXPERIMENT 3.—Two rats were given 0.35 gm. per kg. They weighed 0.107 kg. and 0.100 kg.; neither showed any symptoms.

6. Kobert: Intoxikationen, p. 146.

EXPERIMENTS ON RABBITS

EXPERIMENT 1.—A rabbit of 1.0 kg. was given 0.43 gm. per kg. without exhibiting any symptoms.

EXPERIMENT 2.—A rabbit of 0.90 kg. was given 0.50 gm. per kg.; no effect.

EXPERIMENT 3.—A rabbit of 0.70 kg. was given 0.55 gm. per kg.; no effect.

EXPERIMENT 4.—Three rabbits each received an injection of 0.75 gm. per kg.

Rabbit	Wt. in Kg.	
1.	0.78	no effect.
2.	1.34	dead in 1:40.
3.	0.82	reflexes increased (1:39); dead 1:54

EXPERIMENT 5.—A rabbit of 0.86 kg. was given 1 gm. per kg. It died in 2:15 without convulsion.

EXPERIMENTS WITH SODIUM PARACRESOTINATE AND SALICYLATE

There being a possibility of greater toxicity in a mixture of paracresotinate with salicylate, a 10 per cent. solution was prepared containing paracresotinate of sodium one part and natural sodium salicylate three parts. The following experiments were performed on rats:

EXPERIMENT 1.—Two rats were given each 0.35 gm. per kg. of the mixture. One weighed 0.096 kg. and the other 0.140 kg. Neither was affected in any way.

EXPERIMENT 2.—Two rats, weighing 0.155 kg. and 0.100 kg. were given 0.50 gm. per kg. The larger was not affected at all; the smaller had a convulsion in 0:35 and died in 1:10.

The toxicity of sodium paracresotinate and of its mixture with sodium salicylate is shown in the following table:

Rats:—	Dose (per kg.) and Mortality		
Salicylate	0.65 gm.=7/8= 88%	0.5 gm.=1/7 =14%	0.35 gm.=0/8=0 %
Paracresotinate..		0.45-0.5 gm.=4/8 =50%	0.35 gm.=0/2=0 %
Mixture		0.5 gm.=1/2 =50%	0.35 gm.=0/2=0 %
Rabbits:—			
Salicylate	1.6 gm.=3/3=100%	1.4-1.14 gm.=9/14=47%	1.0 gm.=1/4=25%
Paracresotinate..	1.1 gm.=1/1=100%	0.75 gm=2/7 =67%	0.43-0.55 gm.=0/3=0 %

This table indicates that the paracresotinate is more toxic than the salicylate.[7] The difference for rats, although distinct, is small. For rabbits it seems about 50 or 100 per cent. more toxic, but considering the variability of this animal in the experiments on salicylates, the above data are too meager for an exact estimate. The mixture does not exhibit a higher degree of toxicity than either of its components.

Charteris,[8] experimenting with paracresotic acid on rabbits, observed complete paralysis in 2:30 after injecting 0.342 gm. per kg. and death thirty minutes later. The effects he describes can be explained on the basis of his having used the free acid and alcohol. To compare an alcoholic solution of free creosotic acid with an aqueous solution of sodium salicylate is, of course, not permissible.

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7. Cushny (Pharmacology and Therapeutics, 1910, p. 472, note) states that sodium paracresotinate is a little less toxic than sodium salicylate.

8. Brit. Med. Jour., 1891, i, 695.

V.—CONCLUSIONS

The conclusions to be drawn from the experiments are as follows:

1. No differences were detected between the brands of natural and synthetic salicylate examined, although the synthetic samples were the cheapest obtainable on the market.

2. Sodium paracresotinate is not very much more toxic than sodium salicylate.

3. Mixtures of paracresotinate of sodium with natural sodium salicylate do not exhibit greater toxicity than the components; hence, impurities of paracresotinate are probably of no great practical importance.

4. The symptoms of poisoning by sodium salicylate, administered hypodermically, are early vomiting (central), reflex irritability and convulsions terminating in death from asphyxia (after acutely fatal doses within six hours; after just fatal doses, in eighteen hours).

5. The emetic dose for cats is less than 0.6 gm. per kg.; the convulsive dose for cats is from 0.9 to 1.1 gm. per kg., for rats from 0.65 to 0.75 gm. per kg., and for rabbits from 1.14 to 1.6 gm. per kg.; the surely fatal dose for cats is less than 0.8 or 0.9 gm. per kg., for rats 0.65 gm. per kg. and for rabbits 1.6 gm. per kg.

6. The idiosyncrasies are moderate, being most conspicuous in rabbits and least in rats; hence, rats are best adapted for comparative tests.

I would be glad to receive from physicians and others, samples (1 oz. or even 1/3 oz.) of salicylates that have produced untoward effects or have given grounds for suspicion. These, together with a description of the clinical findings, should be sent to me, care of University of Virginia.

I wish to thank Dr. Torald Sollmann, by whom the subject of this paper was assigned to me, for placing the literature at my disposal, for confirming my observations in certain instances, and for invaluable assistance in compiling the data; and Dr. Pilcher and Mr. Hanzlik for confirming many of the observations.

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LEUKOCYTIC ENZYMES IN LEUKEMIA IN NEUTRAL MEDIA *

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The enzymes which have been found in the leukocytes in leukemia are of three kinds—proteolytic, oxidizing and lipolytic.

A protease has been reported in chronic myeloid leukemia by a number of observers. Erben,[1] in studying autolysis of leukemic blood, obtained evidence of protein digestion which he suspected was due to an enzyme contained in the neutrophilic cells; he was, however, unable to demonstrate the source of the ferment satisfactorily, but assumed that the neutrophils furnished it, since he could find no autolysis in lymphoid leukemia. Schumm[2] demonstrated that the incoagulable nitrogen ("albumoses") of leukemic blood resulted from enzymotic activity, though the source of the enzyme was not stated. The occurrence of autolysis in the blood of chronic myeloid leukemia was further confirmed by Pfeiffer,[3] who studied material from two cases. He also showed that bloods presenting a leukocytosis underwent autolysis, though less rapidly than leukemic bloods, a fact which he explained by the smaller number of neutrophilic leukocytes in the former. Müller and Jochmann,[4] by the use of their well-known Löffler serum plate method, showed that proteolysis takes place with myeloid leukemic blood, but not with lymphoid leukemia. Stern and Eppenstein[5] arrived at conclusions similar to those of Müller and Jochmann[4]; the leukocytes from chronic myeloid leukemia liquefied gelatin rendered slightly alkaline, whereas no liquefaction occurred if the blood from lymphoid leukemia (lymphocytes 96 per cent.) were substituted.

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* From the Clinical Laboratory, the Johns Hopkins University and Hospital.
* Presented before the American Society for the Advancement of Clinical Investigation at Atlantic City, May 8, 1911.

1. Erben, F.: Vorläufige Mittheilung über die Bildung uncoagulabler Eiweisskörper im leukämischen Blute, Wien. klin. Wchnschr., 1902, xv, 276; Ueber die Ursache der Peptonbildung im leukämischen Blute, Ztschr. f. Heilk., 1903, xxiv (Abt. f. inn. Med.), 70.

2. Schumm, O.: Ueber ein proteolytisches Ferment im Blute bei myelogener Leukämie, Beitr. z. chem. Physiol. u. Pathol., 1904, iv, 442.

3. Pfeiffer, T.: Ueber Autolyse leukämischen und leukocytotischen Blutes, Wien. klin. Wchnschr., 1906, xix, 1249.

4. Müller, E., and Jochmann, G.: Ueber eine einfache Methode zum Nachweis proteolytischen Fermentwirkungen, nebst einigen Ergebnissen, besonders bei der Leukämie, München. med. Wchnschr., 1906, liii, 1393.

5. Stern, R., and Eppenstein: Ueber Fermentwirkungen der Leukocyten, Sitz. d. schles. Ges. f. vaterländ. Cultur. Autoreferat in Biochem. Centralbl., 1906-7, v, 492.

Owing to the hyperplasia of the bone-marrow and the metaplasia in the viscera in leukemia, it is not surprising that fermentative activity similar to that of the blood should have been found in these tissues. Schumm[6] demonstrated autolysis of the spleen in a case of "acute leukemia." In splenomyelogenous leukemia he found proteolysis in both spleen and bone-marrow. A proteolytic enzyme[7] has been found in the bone-marrow and spleen, to a much less extent in the lymph-glands (depending on the degree of the myeloid metaplasia) in chronic myeloid leukemia by Jochmann and Ziegler.[8] In chronic lymphoid leukemia Jochmann and Ziegler find a proteolytic ferment in the marrow of the ribs and vertebræ, "showing," they say, "that many marrow cells were also present." The spleen from the same case showed no digestive power at all, the same result being obtained also with spleens from two cases of "pseudoleukemia." In acute myeloid leukemia their findings[9] are like those in chronic myeloid.

In view of these findings, it was supposed that proteolysis was a distinctive attribute of the granular (i. e., neutrophilic) leukocytes, one by which they might be distinguished from the non-granular white cells. Nevertheless, Longcope and Donhauser[10] demonstrated beyond question a proteolytic enzyme in the leukocytes of a case of "acute, large-celled lymphatic leukemia,"[11] showing that at least certain types of non-granular leukocytes do not differ biologically in this respect from the granular.

In the leukocytes from the same case, Longcope[12] found a slight lipolytic activity, as determined by the ethyl butyrate method. In a case of "mixed-celled leukemia, lymphocytes predominating," Bergel[13] demonstrated lipase by means of his wax-plate method, the quantity exceeding that found when normal blood was used.

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6. Schumm, O.: Ueber die Autolyse der leukämischen Milz, Beitr. z. chem. Physiol. u. Pathol., 1903, iii, 576; Beitrag zur Kenntniss der Autolyse. II. Ueber die Autolyse des leukämischen Knochenmarks, ibid, 1903, vii, 175.

7. It is a matter of some interest that the enzyme retained its activity after preservation of three years' duration in formalin and after twelve years in alcohol.

8. Jochmann, G., and Ziegler, C.: Ueber das Leukocytenferment in Milz, Lymphdrüsen, und Knochenmark bei Leukämie und Pseudoleukämie, München. med. Wchnschr., 1906, liii, 2093.

9. Ziegler, C., and Jochmann, G.: Zur Kenntniss der akuten myeloiden Leukämie, Deutsch. med. Wchnschr., 1907, xxxiii, 749.

10. Longcope, W. T., and Donhauser, J. L.: A Study of the Proteolytic Ferments of the Large Lymphocytes in a Case of Acute Leukemia, Jour. Exper. Med., 1908, x, 618.

11. Dr. Longcope informs us that the case reported by him is what is now frequently designated "myeloblastic leukemia."

12. Personal communication.

13. Bergel, S.: Fettspaltendes Ferment in den Lymphocyten, München. med. Wchnschr., 1909, lvi, 64.

The presence of an oxidizing ferment in myeloid leukemic blood has been demonstrated by Meyer,[14] who showed conclusively that it is derived from the neutrophilic leukocytes and, further, that it is present in the normal neutrophilic cells of the blood and of pus. It is not found in lymphoid leukemia. Other observers have amply substantiated Meyer's findings.

That the neutrophilic leukocytes in non-leukemic states in all probability contain a proteolytic enzyme was established by F. Müller[15] in his classical study on autolysis of pneumonic exudates. Achalme[16] suspected that pus cells contain a proteolytic ferment, but failed to demonstrate it conclusively since he did not employ cells entirely freed from serum. Opie,[17] however, proved that the pus cells of pleural exudates, produced experimentally in dogs, contain a protease which he has designated "leukoprotease." By adding a suspension of washed cells to a preparation of ox-serum, heated to destroy the antiferment, he was able to study quantitatively the extent of the enzymotic activity and found that the greatest proteolysis occurred in weakly alkaline media. He has obtained similar results with bone-marrow cells.[18] Jochmann and Lockemann,[19] with qualitative tests, have substantiated Opie's findings.

Achalme,[16] furthermore, found evidence pointing to the existence of lipase, amylase, casease, and oxidase in pus. The amylase converted starch into a reducing sugar "which seemed to be maltose." After filtering the pus, the residue on the filter possessed greater amylolytic activity than the filtrate, from which fact Achalme concluded that the enzyme originated in the cells. Apparently, no one has repeated Achalme's work on lipase and amylase in pus, nor did Achalme take into account the possible effect of antiferments in the serum.

No observations are on record as to the ferments of the lymphocytes of normal blood. With lymphoid tissues, such as the spleen and lymphatic glands, and in tuberculous pus (lymphocytes predominating), studies have been made. Thus, Hedin and Rowland[20] have demonstrated

14. Meyer, E.: Beiträge zur Leukocytenfrage, München. med. Wchnschr., 1903, l, 1489.

15. Müller, F.: Ueber die Bedeutung der Selbstverdauung bei einigen krankhaften Zuständen, Verhandl. d. xx. Congr. f. inn. Med., Wiesbaden, 1902.

16. Achalme: Recherches sur la présence de ferments solubles dans le pus, Compt. rend. Soc. de Biol., 1899, li, 568.

17. Opie, E. L.: Enzymes and Anti-Enzymes of Inflammatory Exudates, Jour. Exper. Med., 1905, vii, 316; Solution of Tissue with Abscess, ibid., 1906, viii, 536.

18. Opie, E. L.: The Presence in the Bone-Marrow of Enzymes Resembling those of the Leukocytes, ibid, 1905, vii, 759.

19. Jochmann, G., and Lockemann, G.: Darstellung und Eigenschaften des proteolytischen Leukocytenfermentes, Beitr. z. chem. Physiol. u. Pathol., 1908, xi, 449.

20. Hedin, S. G., and Rowland, S.: Ueber ein proteolytisches Enzym in der Milz, Ztschr. f. physiol. Chem., 1901, xxxii, 341.

a proteolytic enzyme in the spleen of the ox, horse, sheep and hog which exhibits its maximal activity in acid media, showing feeble digestive power in neutral or alkaline solutions. They find the same or a similar ferment[21] in the lymph-glands and certain other organs. Later Hedin[22] described a proteolytic enzyme in the spleen of the ox which was active principally in an alkaline medium and to which he gave the name lieno-alpha-protease, while he designated the ferment active in an acid medium lieno-beta protease. The products of the protein digestion of each of these enzymes have been investigated by Leathes[23] and by Cathcart.[24]

Lipase has been shown by Bergel[13] to exist in tuberculous pus, the spleen and lymphatic glands, and in the exudate resulting from subcutaneous injection of old tuberculin in guinea-pigs.

To summarize the results in literature briefly, it has been shown that the normal and pathological neutrophilic leukocytes and myeloblasts contain a proteolytic enzyme which is most active in alkaline media; that neutrophilic cells contain an oxidase and probably a lipase and an amylase; that myeloblasts contain a lipase. In lymphoid tissues, two proteases and a lipase have been shown to exist. In leukemia, leukoprotease has been demonstrated in the myeloid variety of the disease (including a case of myeloblastic leukemia), while it has been absent in chronic lymphoid leukemia. Lipase has been demonstrated in two cases of myeloid leukemia, and oxidase in all myeloid cases observed in which the neutrophilic cells were present in excess.

It seemed to us desirable to examine the enzymes of leukemic leukocytes in greater detail, including a repetition of the work that had already been done and a search for other enzymes. It has been our good fortune to have the opportunity of studying the blood of six leukemics within the last two years, our material comprising two cases of acute myeloid leukemia, two of chronic myeloid and two of chronic lymphoid leukemia. We have also made parallel experiments on the cells obtained from empyema pus.

In the cases of chronic myeloid and chronic lymphoid leukemia, blood was obtained by passing a needle directly into an arm vein. The needle was connected with an aspirating bottle containing 500 c.c. of 0.85 per cent. sodium chlorid and 1.5 per cent. sodium citrate solution to prevent clotting. About 200 c.c. of blood was aspirated in each instance. The material was then centrifugalized at high speed to throw down the corpuscles. The supernatant liquid was

21. Hedin, S. G., and Rowland, S.: Untersuchungen über das Vorkommen von proteolytischen Enzymen in Thierkörper, ibid., 1901, xxxii, 531.

22. Hedin, S. G.: Investigations on the Proteolytic Enzymes of the Spleen of the Ox, Jour. Physiol., 1904, xxx, 155.

23. Leathes, J. B.: The Products of the Proteolytic Action of an Enzyme Contained in the Cells of the Spleen, Jour. Physiol., 1902, xxviii, 360.

24. Cathcart, E. P.: The Products of Digestion of the Proteolytic Spleen Enzyme Acting in an Alkaline Medium, Jour. Physiol., 1905, xxxii, 299.

removed and the leukocytes which separated to form a creamy layer above the red corpuscles were transferred by a pipette to fresh tubes. By repeating this process it was possible to obtain the leukocytes reasonably free from erythrocytes. Finally, the cells were washed three times in physiological salt solution to remove the plasma with its enzymes and antienzymes, and were then suspended in 0.85 per cent. salt solution, two volumes of the latter being added to one volume of corpuscles. The suspension was kept in the ice-chest under toluol until used (usually not more than two days). In the two acute myeloid leukemias the blood was obtained post mortem, in the one case by aspiration from the heart, in the other from the heart and great vessels during autopsy.

TABLE 1.—BLOOD EXAMINATION FROM EACH CASE

Case.	Hb.	R. B. C.	W. B. C.	Lymphocytes.	Large monos. and Transit.	Polymorph. neutrophil.	Polymorph. eosinophil.	Mastzellen.	Myelocytes, neurophil.	Myelocytes, eosinophil.	Myelocytes, basophil.	Myeloblasts.
				%	%	%	%	%	%	%	%	%
1. Ac. myel. leuk..... H.	..	976,000	31,000	7.6	2.4	28.0	1.6	0.0	48.6	1.0	0.0	10.8
2. Ac. myel. leuk..... S.	25	1,008,000	28,600	14.4	20.6	12.4	0.0	0.0	3.0	0.0	0.0	66.4*
3. Chr. myel. leuk..... R.	45	2,660,000	632,000	0.4	0.0	53.9	5.7	0.0	39.4	0.4	0.0	0.0
4. Chr. myel. leuk..... C.	46	2,800,000	313,000	2.8	1.0	52.8	2.1	6.4	31.4	3.0	0.2	0.0
5. Chr. lymph. leuk..... E.	54	2,276,000	640,000	96.6	0.7	0.5	0.8	0.0	1.3	0.0	0.0	0.0
6. Chr. lymph. leuk..... F.	87	5,200,000	138,000	74.0	9.0	17.0	9.2	0.0	0.0	0.0	0.0	0.0

* Thirteen per cent. with convoluted nuclei, of which about one-eighth contain neutrophilic granules (atypical myelocytes).

In each case the leukocytes were tested for the presence of the following types of endo-enzyme: protease, lipase, amylase, maltase, invertase, lactase, a glycolytic enzyme, and oxidase. Since the number of ferments tested for was comparatively large and the quantity of leukocytic suspension at our disposal relatively small, it was impossible to study the effects in more than one reaction. It was, therefore, decided to limit the observations for the present study to possible action in *neutral media*.

For the greater ease in interpreting results it has seemed desirable to give a blood examination from each case (Table 1), including differential count.

PROTEASE

Leukoprotease was tested by the method of Opie[25] as employed by Longcope and Donhauser,[10] except that we substituted ascitic or pleural fluid for ox-serum or horse-serum.

25. Opie, E. L.: The Enzymes in Phagocytic Cells of Inflammatory Exudates, Jour. Exper. Med., 1906, viii, 410.

Method.—One part of puncture fluid is diluted with 2 parts of 0.85 per cent. sodium chlorid solution; the mixture is heated for one-half hour on a water bath at a temperature of 75 to 80 C. to destroy any enzymes or antienzymes present. It acquires a milky opalescence. After cooling, to 10 c.c. of this fluid in a small Erlenmeyer flask or test-tube, 1 c.c. of 33 per cent. suspension of leukocytes and 1 c.c. of toluol are added. The flask or test-tube is corked, sealed with paraffin and placed in an incubator for five days at a temperature of 37 C. It is then removed, 10 c.c. of 16 per cent. solution of magnesium sulphate and a few drops of dilute acetic acid added to the flask and the mixture is boiled. The acid is now neutralized and the contents of the flask boiled again. Finally, the coagulable protein is removed by filtration, flask and filter being washed thrice with distilled water. The filtrate and washings are collected directly into Kjeldahl flasks and the quantity of incoagulable nitrogen estimated by the Kjeldahl method. The flasks are always set up in duplicate. For control, the experiment is repeated in the same way, substituting 1 c.c. of *boiled* leukocytic suspension for the active unboiled suspension. The controls were also carried out in duplicate. The difference in quantity of incoagulable nitrogen in the "active" and control experiments gives the measure of proteolysis, if present.

TABLE 2.—PROTEIN. (EXPERIMENTS 1 AND 3 ACTIVE, EXPERIMENTS 2 AND 4 CONTROLS)

(The figures in the second column represent c.c. of $\frac{n}{10}$ H_2SO_4 neutralized.)

Case.	No.	$\frac{n}{10}$ c.c.—H_2SO_4	Result.
1. Ac. myel. leuk. H.	1)	4.55	Positive.
	2)	2.55	
	3)	4.25	
	4)	2.25	
2. Ac. myel. leuk. S.	1)	4.45	Positive.
	2)	2.55	
	3)	5.05	
	4)	2.05	
Empyema pus	1)	3.25	Positive.
	2)	0.9	
	3)	3.45	
	4)	1.45	
3. Chr. myel. leuk. R.	1)	7.5	Doubtful; apparently negative. Probably unboiled cells used in 2 by mistake.
	2)	6.35	
	3)	6.75	
	4)	lost	
4. Chr. myel. leuk. C.	1)	lost	Positive.
	2)	2.4	
	3)	6.9	
	4)	2.9	
5. Chr. lymph. leuk. F.	1)	7.3	Positive.
	2)	1.7	
	3)	6.5	
	4)	0.7*	
6. Chr. lymph. leuk. E.	1)	2.2	Positive.
	2)	0.1	
	3)	3.4	
	4)	0.1	

* No leukocytes added.

In all cases, there was evidence of proteolysis (Table 2), with the possible exception of Case 3. The comparatively low values are possibly explained by the fact that the optimal medium for leukoprotease (of the neutrophilic cells) is alkaline, whereas we used only neutral media. The results in the two cases of chronic lymphoid leukemia are surprising, in view of the negative findings reported in literature. Whether this

ferment is identical with the leukoprotease of the neutrophilic leukocytes is not clear. Possibly we are dealing with a ferment analogous to Hedin's lieno-beta-protease,[22] or to that described by Opie[25] in the macrophages or larger mononuclear cells of exudates and by Opie and Barker[26] in the epithelioid cells of tuberculous tissue, all of these acting best in an acid medium, though still active in neutral solution. Until they are proved dissimilar, there is no reason for assuming that the proteases of neutrophilic leukocytes and of leukemic lymphocytes are not identical. When material becomes available, however, we hope to investigate more fully the protease of the lymphocytes in chronic lymphoid leukemia.

TABLE 3.—ETHYL BUTYRATE. (EXPERIMENTS 1 AND 3 ACTIVE, EXPERIMENTS 2 AND 4 CONTROLS)

(The figures represent the c.c. of $\frac{n}{20}$ NaOH required to neutralize.)

Case.	No.	$\frac{n}{20}$ c.c.—alkali	Result.
1. Ac. myel. leuk. H.	1)	3.25	Positive.
	2)	0.8	
	3)	2.85	
	4)	0.8	
2. Ac. myel. leuk. S.	1)	3.0	Positive.
	2)	0.6	
	3)	3.3	
	4)	0.6	
Empyema pus	1)	0.9	Weak action?
	2)	0.4	
	3)	0.95	
	4)	0.4	
3. Chr. myel. leuk. R.	1)	3.2	Positive.
	2)	1.05	
	3)	3.3	
	4)	1.75?	
4. Chr. myel. leuk. C.	1)	2.0	Positive.
	2)	0.1*	
	3)	1.8	
	4)	0.1*	
5. Chr. lymph. leuk. F.	1)	2.55	Positive.
	2)	0.65	
	3)	3.1	
	4)	0.25*	
6. Chr. lymph. leuk. E.	1)	0.6	Weak action?
	2)	0.1†	
	3)	0.6	
	4)	0.1†	

* No boiled cells. † No boiled cells added.

LIPASE

The ethyl butyrate method of Kastle and Loevenhart[27] was employed in testing for lipase.

Method.—To 0.5 c.c. of ethyl butyrate in a small test-tube were added 0.5 c.c. of a 33 per cent. suspension of leukocytes and 0.5 c.c. toluol. The tubes were corked, sealed with paraffin and incubated at 37 C. for five days. All experi-

26. Opie, E. L., and Barker, B. I.: Enzymes of Tuberculous Exudates, Jour. Exper. Med., 1909, xi, 686.

27. Kastle, J. H., and Loevenhart, A. S.: Concerning Lipase, the Fat-Splitting Enzyme, and the Reversibility of its Action, Am. Chem. Jour., 1900, xxiv, 491.

ments were set up in duplicate. Controls in duplicate were identical, except that they contained a boiled suspension of leukocytes. At the completion of incubation the contents of the tubes were titrated with twentieth-normal sodium hydrate in alcohol, phenolphthalein being used as the indicator.

Evidence of splitting of ethyl butyrate was obtained in five instances (Table 3). It was doubtful in empyema pus and in Case 6. Since the cells of myeloid leukemia exhibit lipolytic activity, Bergel's[13] contention that this property differentiates lymphocytes from neutrophilic cells biologically becomes untenable. Indeed, his own positive result in a case of "mixed-celled leukemia, lymphocytes predominating" is direct evidence against his view, since it is generally recognized that cases which were formerly designated as "mixed-celled leukemias" are in reality myeloid leukemias presenting an unusually large number of non-granular bone-marrow cells (lymphoid cells, myeloblasts, etc.). Longcope's finding confirms that of Bergel, and is identical with our results.

TABLE 4.—STARCH. (EXPERIMENTS 1 AND 3 ACTIVE, EXPERIMENTS 2 AND 4 CONTROLS)

Case.	(1:50) Lugol's sol.	Polariscope 100 mm. tube.	Fehling's	Result.
1. Ac. myel. leuk..... H.	1) Blue	0	0	None.
	2) Blue	0	0	
	3) Blue	0	0	
	4) Blue	0	0	
2. Ac. myel. leuk..... S.	1) Blue	0	0	None.
	2) Blue	0	0	
	3) Blue	0	0	
	4) Blue	0	0	
Empyema pus.....	1) Blue	(0.45=)0.9	Quick reduc...	Positive.
	2) Blue	(1.0 =)2.0	No reduction..	
	3) Blue	(0.6 =)1.2	Quick reduc...	
	4) Blue	(1.1 =)2.2	No reduction..	
3. Chr. myel. leuk.... R.	1) Blue	(0.7 =)1.4	Quick reduc...	Positive?
	2) Blue	(1.1 =)2.2	Slight reduc...	
	3) Blue	(0.7 =)1.4	Quick reduc...	
	4) Blue	(0.7 =)1.4	Quick reduc.†..	
4. Chr. myel. leuk.... C.	1 and 3) no color	(0.85=)0.7	Quick reduc...	Positive.
	2 and 4) blue..	(0.3 =)0.6	No reduction..	
5. Chr. lymph. leuk... F.	1) No color....	(0.8 =)1.6	Slow reduc.....	Positive.
	2) Blue	(0.85=)1.7	No reduc.‡.....	
	3) No color....	(1.2 =)2.4	Quick reduc.‡..	
	4) Blue	(0.4 =)0.8*	No reduction..	
6. Chr. lymph. leuk... E.	1) Blue	(0.75=)1.5	Quick reduc...	Positive.
	2) Blue	(0.3 =)0.6	No reduction..	
	3) Blue	(0.8 =)1.6	Quick reduc...	
	4) Blue	Filtrate lost	Lost	

* No suspension used—simply starch : toluol.
† Probably active. ‡ Does not ferment. ‡Ferments.

AMYLASE

Method.—A 1 per cent. starch-water was boiled two or three minutes and allowed to cool to room temperature. To 10 c.c. of the starch-water were added 1 c.c. of a 33 per cent. suspension of leukocytes and 1 c.c. of toluol. As in the previous experiments, two active and two control tubes were prepared in each case. The tubes were sealed with paraffin and incubated five days at 37 C. At the end of this time the contents of each tube were filtered until the filtrate came through clear. The material remaining on the filter was then tested with Lugol's solution (1:50) for the iodin-starch reaction. The filtrate was exam-

ined polariscopically to determine whether there was increased dextrorotation in the active tubes as compared with the controls, since maltose and dextrose, the end-products to be expected from starch, might be disclosed in this manner. After completing the polariscopic examination, a portion of the filtrate was tested with Fehling's solution, and in a few instances subjected to Cippolina's modification of the phenylhydrazin test. In addition (after obtaining some positive results), large quantities of material (one case chronic myeloid leukemia; pus) were incubated (Table 5). A part of the filtrate was then examined polariscopically before and after fermentation with yeast. The remainder was used for the phenylhydrazin test. The crystals resulting were purified by recrystallizing several times from boiling 60 per cent. alcohol, dried, and 0.2 gm. dissolved in 4 c.c. pyridin and the solution diluted with 6 c.c. absolute alcohol. The solution was then examined polariscopically. Finally, the melting-point of the crystals was determined (in one case of chronic myeloid leukemia), according to the method of Menge.[28]

TABLE 5.—STARCH

Case.	Method.
Empyema pus...	400 c.c. 1 per cent. starch-water + 40 c.c. 33 per cent. leukocyte suspension + toluol q. s. Incubator at 37 C. for five days. Polariscope 100 mm. tube. Filtrate unfermented .....(0.6=)1.2 Filtrate fermented .....(0.0=)0.0 Phenylhydrazin test positive. 0.056 gm. crystals dissolved in 4 c.c. pyridin + 6 c.c. absolute alcohol (100 mm. tube)=levorotation 0.3. Calculated for 0.2 gm. crystals= —1.07.
4. Chr. myel. leuk. C.	1) 400 c.c. 1 per cent. starch water + 58 c.c. of 33 per cent. leukocyte suspension + toluol q. s. Incubator at 37 C. two weeks. 2) 100 c.c. 1 per cent. starch-water + 10 c.c. boiled suspension + toluol. Incubator 2 weeks. (Control.) 100 mm. tube Lugol's Sol. Polariscope. Fehling's. 1) No color.....(0.85=)1.7....Immediate reduction. 2) Blue color....(0.3 =)0.6....No reduction. Phenylhydrazin test on filtrate (1) positive. 0.2 gm. crystals dissolved in 4 c.c. pyridin + 6 c.c. absolute alcohol in 100 mm. tube gives levorotation= —1.3.

The results obtained in testing for amylase require discussion before attempting to interpret them. Cases 1 and 2 may be excluded, since, owing to an error, the starch solution used was not boiled. The iodin reaction for starch proved helpful only when there was complete hydrolysis of the starch, as in Cases 5 and 6, Table 4. The polariscopic findings proved even more confusing. In certain cases the controls gave the greater dextrorotation (Case 3 and empyema pus). That this was not due to a reducing sugar is proved by the negative Fehling's test. The nature of the dextrorotatory body in the controls is unknown. From the outcome of the iodin test it is probable that the quantity of leukocytic suspension used has been too small or that the incubation was too brief; with relatively larger amounts, it is probable that the destruction of starch would be complete, making the iodin reaction of greater value. In reading the findings in Table 4, we wish to lay special emphasis on the

28. Menge, G. A.: A Study of Melting-Point Determinations, Bull. No. 70, Hyg. Lab., U. S. P. H. and M.-H. S., 1910.

outcome of Fehling's test, since this alone shows consistent results. The one exception is Tube 4, Case 3, a control, in which a quick reduction occurred. Since the polariscopic reading agrees with those of Tubes 1 and 3 (active), it is probable that an error occurred in setting up the tubes, by which active suspension was substituted for the boiled.

TABLE 6.—MALTOSE. (EXPERIMENTS 1 AND 3 ACTIVE, EXPERIMENTS 2 AND 4 CONTROLS)

Case.	No.	Polariscope 100 mm. Tube.	Result.
1. Ac. myel. leuk.... H.	1)	(0.75=)1.5	Positive.
	2)	(1.4 =)2.8	
	3)	(0.85=)1.7	
	4)	Lost	
2. Ac. myel. leuk.... S.	1 & 3)	(0.5 =)1.0	Positive.
	2 & 4)	(1.3 =)2.6	
Empyema pus....	1)	(1.4 =)2.8	Positive.
	2)	(2.6 =)5.2	
	3)	(1.4 =)2.8	
	4)	(2.6 =)5.2	
3. Chr. myel. leuk.... R.	1)	(1.2 =)2.4	Positive.
	2)	(2.15=)4.3	
	3)	(1.2 =)2.4	
	4)	(2.1 =)4.2	
4. Chr. myel. leuk.... C.	1)	(0.8 =)1.6	Positive.
	2)	(1.4 =)2.8	
	3)	(0.7 =)1.4	
	4)	(1.4 =)2.8	
5. Chr. lymph leuk.... F.	1)	(1.7 =)3.4	Positive.
	2)	(2.5 =)5.0	
	3)	(1.9 =)3.8	
	4)	(2.9 =)5.8*	
6. Chr. lymph. leuk.... E.	1)	(1.2 =)2.4	Positive weakly. (Cells preserved with chloroform. U. S. P. Ferments probably inactivated.
	2)	(1.5 =)3.0	
	3)	(1.2 =)2.4	
	4)	(1.5 =)3.0	

* No W. B. C. suspension in 4.

The findings given in Table 4, we believe, are highly suggestive, though perhaps not absolutely conclusive of the presence of an amylase. Lack of material prevented further study of the point, except with the empyema pus and with Case 4, chronic myeloid leukemia, in which the patient's death eight months after the observations reported in Table 4, enabled us to obtain an additional supply of leukocytes. The details of these experiments are given in Table 5. In both instances the phenylhydrazin test yielded characteristic yellow needles arranged in sheaves. With the leukocytes from pus, the purified crystals dissolved in pyridin and alcohol gave a levo-rotation of 1.07, calculated for 0.2 gm. of crystals. Since phenylglucosazone crystals should give levo-rotation of 1.3, it is reasonably certain that these are the crystals obtained. Phenylmaltosazone, the only other product which would be probable as a result of starch digestion, is dextrorotatory when dissolved in pyridin and alcohol, and is, therefore, excluded or present only in minute traces. In the case of the myeloid leukemic leukocytes, it is established beyond all doubt that the starch has been converted quantitatively into glucose. The crystals

obtained by the phenylhydrazin test were again characteristic microscopically. After purification and drying, 0.2 gm. of the crystals, dissolved in pyridin and alcohol, gave a levo-rotation of 1.3, which proves them to be the crystals of glucose. Three determinations of the melting-point[29] of these crystals gave the following results: The compound began to darken at 202.3, 203.3 and 203.3 C.; it melted to a dark brown oily smear at 209.6 to 210.1, 210.1 to 210.6 and 210.1 to 210.6 C. respectively. From what is known of amylase, it is probable, of course, that this result, i. e., the conversion of the starch to glucose, is the result of the action of two enzymes, the one, amylase, changing the starch to the disaccharid, maltose, a second ferment, maltase, being responsible for the production of the glucose.

From the above considerations, we can affirm the existence of amylase in the neutrophilic cells of pus and of chronic myeloid leukemia and are reasonably certain of its presence in the lymphocytes of chronic lymphoid leukemia. That the leukocytes are to be reckoned with as at least one of the producers of blood amylase seems clear. Moeckel and Rost,[30] in a recent review on the "origin and significance of the amylolytic ferments of the blood," dismiss the leukocytes with a word and assume that they are of no importance. Indeed, there has been no evidence in the literature to the contrary, so far as we can learn, excepting the observations of Achalme,[16] already noted, and experiments made by Haberlandt,[31] which seemed to show that the polymorphonuclear leukocytes of the frog and the mouse may cause an increase in the quantity of amylase in the blood plasma.

MALTASE

To determine whether maltose has been converted into glucose, advantage was taken of the fact that maltose is the more powerfully dextrorotatory of the two sugars. Therefore, conversion of maltose into glucose should be indicated by a diminution of the dextrorotation in the active tubes as compared with the controls.

Method.—Ten c.c. of a maltose solution (the concentration varying somewhat, but being the same in a given series of observations) were treated with 1 c.c. of a 33 per cent. suspension of leukocytes and 1 c.c. of toluol, corked and paraffined, incubated five days at 37 C., and finally, after filtration, examined polariscopically.

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29. We desire to express our thanks to Dr. George A. Menge of the U. S. Public Health and Marine Hospital Service, Washington, for his kindness in determining the melting-points reported here. The readings are corrected for emergent stem and calibration. It will be noticed that the "decomposition point" coincides approximately with the melting-point usually given for phenylglucosazone, whereas the *true* melting-point is higher. For a discussion of this, see Menge's publication (note 28).

30. Moeckel, K., and Rost, F.: Ueber den Ursprung und die Bedeutung des amylolytischen Blutfermentes, Ztschr. f. physiol. Chem., 1910, lxvii, 433.

31. Haberlandt, L.: Zur Existenz eines diastatischen Leukocytenfermentes, Archiv. f. d. ges. Physiol., 1910, cxxxii, 175.

In Table 6, the consistent results obtained in all instances indicate the presence of maltase in the neutrophilic leukocytes of pus and of acute and chronic myeloid leukemia and in the lymphocytes of chronic lymphoid leukemia. Additional proof of maltase action is furnished by the conversion of starch into glucose through the agency of the leukocytes of pus and of chronic myeloid leukemia, as noted above. The phenylglucosazone crystals which were demonstrated are most probably due to the combined action of amylase and of maltase on starch.

Invertase, lactase, and a glycolytic ferment were totally lacking in all the material examined, so far as could be determined. The method used to detect them was similar to that described for maltase, except that saccharose, lactose and glucose, respectively, were substituted for maltose.

OXIDASE

The guaiac test as applied by Meyer[14] and, in some cases, the phenolphthalin test of Kastle[32] have been used in testing for an oxidase in the leukocytes.

The results were in line with those obtained by Meyer and others. In all instances in which cells with neutrophilic granulations were the predominant ones, a positive reaction took place. Thus, in one case of acute myeloid leukemia (Case 1), in both cases of chronic myeloid leukemia, and with pus cells an oxidase was demonstrable. On the other hand, the two cases of chronic lymphoid leukemia gave no indication of oxidizing either guaiac or phenolphthalin, and Case 2 of acute myeloid leukemia was also negative, owing, no doubt, to the small percentage of granular marrow cells present. Similar findings with acute myeloid leukemia have been reported by a number of observers.

SUMMARY OF RESULTS

The findings recorded above indicate that digestion of protein, starch, maltose and ethyl butyrate may be accomplished by enzymes present in the leukocytes of pus, chronic and acute myeloid leukemia, and chronic lymphoid leukemia in neutral media. No evidence of cleavage of saccharose, lactose, or glucose has been found. We wish particularly to emphasize that a neutral reaction alone has been employed. One cannot foretell what may take place in studying the cells of a lymphoid leukemia in acid and alkaline media, and this seems of special importance with reference to proteolysis.

The uniformity of the leukocytic endo-enzymes in acute and chronic myeloid leukemia on the one hand, and in chronic lymphoid leukemia on the other, is quite unexpected and is not in harmony with the results in

32. Kastel, J. H.: Chemical Tests for Blood, Bull. No. 51, Hyg. Lab., U. S. P. H. and M.-H. S., 1909.

literature nor with the teachings of Naegeli[33] and his followers, who hold that the lymphocytes lack the proteolytic ferment found in the cells of the myeloid series, an important biological difference. That the lymphocytes of chronic lymphoid leukemia contain a proteolytic ferment we have shown. But until further studies can be made of this enzyme, it is impossible to discuss its identity or non-identity with leukoprotease. So far as the present studies go, limited, as they are, to neutral media, it is impossible to discover *any* biological differences between the lymphoid and myeloid cells. Oxidase is of no value, since it is not demonstrable in the non-granular cells of the bone-marrow, at least with guaiac and phenolphthalin. The facts just elicited might be taken as favoring the view that all leukocytes are derived from a single parent cell, but this would be premature, owing to the incompleteness, already alluded to, of the study of proteolysis by the lymphocytes. Furthermore, many of the tissues of the body contain the four enzymes described for the leukocytes.

The occurrence of protease, amylase, maltase, and lipase in the leukocytes is not without physiologic interest. Howell[34] refers to the white corpuscles of the blood as "unicellular glands, the products of their metabolism serving to maintain the normal composition of the blood-plasma." Since it is well established that the plasma contains the enzymes just enumerated, it might be suggested that they possibly constitute a part of the secretion of the leukocytes.

CONCLUSIONS

In *neutral* media, the following conclusions as to the endoenzymes of the leukocytes seem warranted:

1. A protease is present in the lymphocytes of chronic lymphoid leukemia and in the leukocytes of acute and chronic myeloid leukemia and of pus.

2. Lipase occurs in the white cells in the same conditions.

3. It is shown that amylase is contained in the granular leukocytes of pus and of myeloid leukemia, acute and chronic, and in the lymphocytes of chronic lymphoid leukemia.

4. Maltase is likewise a product or constituent of these cells.

5. Digestion of saccharose, lactose and glucose by myeloid or lymphoid cells has not been observed in neutral media.

6. Oxidase is demonstrable in the leukocytes in conditions in which the granular cells of the marrow are present in large numbers.

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34. Howell, W. H.: A. Text-Book of Physiology, First Edition, Philadelphia and London, 1905, p. 406.

33. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Leipzig, 1908, p. 139.

7. Biological differences between myeloid cells and the lymphocytes of chronic lymphoid leukemia have not been demonstrated in neutral media.

8. It is a legitimate inference that in part, at least, the enzymes of the plasma may be derived from the leukocytes.

In conclusion, we desire to express our thanks to Dr. Warfield T. Longcope for his generosity in placing unpublished protocols of experiments at our disposal, and to Dr. L. F. Barker and Dr. W. S. Thayer for permission to study the material in their wards.

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THE COAGULATION-TIME OF THE BLOOD AS AFFECTED BY VARIOUS CONDITIONS

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(*Concluded from p. 716*)

IV. PATHOLOGICAL CONDITIONS OF THE BODY INFLUENCING THE CLOTTING-TIME

There are a number of abnormal conditions probably affecting the coagulability of the blood while it is still in the vessels. I called attention to some of these several years ago.

1. Fever.—The presence of fever apparently exercises no influence on the clotting-time. The latter was unaffected by the patient's temperature in my cases, as will be seen from the following tables. In order to permit of better comparison, all records made with Wright's tubes are also given in parentheses expressed in terms of my method.

Hartman states that the clotting-time is normal at collapse temperature and in fever, having convinced himself through many dozens of tests that temperature changes of 2 to 3 degrees Centigrade do not alter the clotting-time, the latter being the same if the tested person has a temperature of 36 or 38.5 C.

Coleman regards the pyrexia that followed the injection of beta-naphthylamine in two rabbits as the cause of the lengthening of the coagulation-time of the blood that accompanied it, because in a third rabbit similarly injected there was a slight fall in the temperature and practically no alteration in the clotting-time.

2. Hemorrhage.—The influence of hemorrhage will be studied separately according to whether it is traumatic, spontaneous, or occurring in the course of a disease.

A. Traumatic Hemorrhage: It is generally recognized that a shortened clotting-time follows a hemorrhage. Arthus, Hewson, Terroin, Chantemesse, von der Velden, Vierordt and Robertson, Illman and Duncan have definitely shown this to be a fact.

Chantemesse declares that all states accompanying a profound destruction of blood, whether by repeated external hemorrhages or by internal hemolysis, create gradually in the organism a state of spontaneous defense which brings about an augmented intravenous coagulability of the blood, to combat the loss of blood.

TABLE 9.—RELATION BETWEEN THE COAGULATION TIME AND THE PATIENT'S TEMPERATURE

	Normal Cases	—Tuberculosis Cases— (Author's Method)			——Diseases other than Tuberculosis—— (Wright's Tubes)		
	Afebrile	Afebrile	98.6° to 100° F.	Above 100° F.	Afebrile	98.6° to 100° F.	Above 100° F.
No. of cases	20	5	36	36	32	16	17
No. of observations.....	23	5	48	49	32	17	17
Aver. clotting-time (minutes)	8⅔	5¼	5⅒	5	2⅓ (8$^{1}/_{12}$*)	2⅝ (8¼ *)	2⅓ (8$^{1}/_{11}$*)
Max. clotting-time (minutes)	12¼	7½	8½	9⅛	5 (17⅓ *)	4¾ (16½ *)	3¼ (11¼ *)
Min. clotting-time (minutes)	4	2⅛	2½	3	¾ (2$^{1}/_{5}$*)	⅞ (3 *)	1¾ (6 *)

*As expressed in terms of author's method.

According to Hartman a *suddenly* occurring difference in the blood content of the body seems to be necessary for this shortening, because even in patients with a hemorrhage of high grade, if only the hemorrhage were not sudden, but came on gradually, there was not a constant change in the clotting-time. Von der Velden also says that the shortening of the clotting-time can be shown only slightly, if at all, in small hemorrhages or in the long withdrawal of a quantity of blood from the circulation.

It was the experience of Addis that the removal of a pint of blood from a vein for therapeutic purposes was in three cases entirely without influence on the coagulation-time. An acceleration of coagulation was observed, however, in two cases in which large and dangerous hemorrhages occurred.

A markedly shortened clotting-time (three and a half minutes with my method on a dry, clear, moderately warm day, when two normal individuals examined at the same time gave clotting-times of ten and one-quarter and nine and three-quarter minutes, respectively) was observed four days after a tonsillectomy on a healthy man who bled profusely for ten minutes at the time of the operation and later had a secondary hemorrhage lasting seven hours.

Birnbaum and Osten, on the other hand, found considerable retardation of coagulation in the blood of non-menstruating women who had suffered severe hemorrhage, which they explain by the greater water content of the blood in a long bleeding. Insomuch as in severe hemorrhage both the red and white blood-cell counts are diminished, they supposed that likewise with severe blood loss the ferment-making substances are also smaller.

Two of Hartman's cases, that had a marked lengthening of the clotting-time, were explained on the theory that if a hemorrhage is too great, the blood would not have enough time to replace the lost volume of blood by taking water from the intestines or by other provisions for replacing water in the blood. Von der Velden also speaks of a secondary thinning of the blood, its rapidity and extent depending on the speed and nature and also on the amount of the hemorrhage.

Terroine, who followed his bleedings in the dog by reinjections of equal volumes of artificial serum or Locke's fluid, states that if one leaves sufficient space between the bleedings, the blood coagulates spontaneously more and more quickly up to a certain moment, beginning from which coagulation diminishes. By prolonging the experiment one can finally obtain a blood that no longer coagulates spontaneously.

The spontaneous shortening of the clotting-time following a hemorrhage makes one examine very critically evidence as to the action of any therapeutic agent employed for checking hemorrhage.

B. Menorrhagia: The clotting-time in four cases of menorrhagia, taken with my method, averaged eight and one-fifth minutes, a practically normal time. Busse, however, believes hemorrhages of the type of menorrhagia to be symptoms of a general disease, a mild grade of hemophilia frequently with lengthening of the clotting-time.

C. Metrorrhagia: My two cases of metrorrhagia had practically normal clotting-times of eight and one-eighth and eight and one- half minutes respectively. Metrorrhagia, according to Busse, is also often only a symptom of a general disease, a manifestation of hemophilia associated with lengthened coagulation-time.

D. Hemorrhage from a Uterine Fibroid: A patient with a uterine fibroid causing menorrhagia and metrorrhagia had a clotting-time of eleven minutes (my method)—decidedly prolonged.

Chantemesse thinks that the repeated hemorrhages suffered by women with fibroids ought to develop in them a mechanism that for the purpose of spontaneous defense manufactures a blood more coagulable than normal. He found their blood before operation always to coagulate more quickly than normal. The sudden death so common after operations for fibroid he attributes to the formation of thrombi and emboli due to the factor of local stasis, favored by the surgeon's ligature, in a blood already of high coagulability.

E. Hemorrhage from Uterine Carcinoma: Robertson, Illman, and Duncan observed hastened coagulation in hemorrhage from carcinoma of the uterus.

F. Hemoptysis in Pulmonary Tuberculosis: A connection at times between hemoptysis and a hemorrhagic tendency is pointed out by Anders, who observed several cases of early pulmonary bleedings associated with hemorrhage from other mucous outlets, as the stomach and nose. Wright says that in many cases of hemoptysis the hemorrhage is inordinate in quantity and is associated with serious defect of blood coagulability. My studies in relation to blood-spitting in pulmonary tuberculosis are reported below in detail.

There is apparently no change in the clotting-time at the menstrual period in tuberculous women who spit blood at such times. The clotting-time is shorter in patients who have never had a pulmonary hemorrhage than in those who have had one. The influence of a pulmonary hemorrhage in shortening the clotting-time is apparently seen in three cases examined both before and during a hemorrhage which had an average clotting-time of seven and a half minutes before the bleeding and four minutes while it was in progress. The average coagulation-time taken on the third day of a hemorrhage in thirteen cases, moreover, was a little over a third of the average clotting-time of six cases, taken on the first day, or of two clotting-times taken on the second day. On the other hand, hemorrhages that were continuing unabated gave an average time one

and a quarter minutes longer than those that were diminishing. Slight hemorrhages apparently occur in those whose clotting-time is longer than normal, and apparently have no effect in shortening the clotting-time, which is lengthened in such cases both during the hemoptysis and after it has ceased. Streaks of blood in the sputum apparently occur in persons whose clotting-times are only slightly longer than normal, and these seem to have practically no effect on the clotting-time over a period of five days. Whether severe hemorrhages occur chiefly in those whose clotting-times are longer than normal cannot be deduced from my figures —which show a normal clotting-time as the average of six cases within two days of a severe hemorrhage, as it is impossible to eliminate the hemorrhage itself as a factor in shortening the time.

TABLE 10.—HEMORRHAGES IN WOMEN IN RELATION TO THE MENSTRUAL PERIOD

Classification	—Number of— Cases	Tests	—Clotting-Time in Minutes— Average	Highest	Lowest
Menstruating	4	5	5¾	6	4⅞
At menstrual period	2	2	5¾	6¼	5¼
Neither of above	10	16	5⅓	10⅜	3⅜

TABLE 11.—NO HEMORRHAGE WITHIN TWO WEEKS; CASES DIVIDED INTO THOSE OF PATIENTS THAT HAVE NEVER HAD AND THOSE THAT HAVE HAD HEMORRHAGE

Classification	—Number of— Cases	Tests	—Clotting-Time in Minutes— Average	Highest	Lowest
Never had hemorrhage	28	39	4⁷/₇	8⅝	2⅝
Had hemorrhage	34	40	5⁵/₆	10¾	3⅛

TABLE 12.—THE CLOTTING-TIME IN PATIENTS WHO HAVE SPIT BLOOD WITHIN TWO DAYS; CASES DIVIDED ACCORDING TO THE SEVERITY OF THE HEMORRHAGE

Classification	—Number of— Cases	Tests	—Clotting-Time in Minutes— Average	Longest	Shortest
All hemoptysis	27	34	5⁵/₆	8½	2¼
Severe hemorrhage	6	7	5⅓	7⅝	2¼
Slight hemorrhage	6	7	6⅛	8½	2⅞
Streaks of blood	15	20	5⅝	7¾	3⅝

TABLE 13.—HEMORRHAGE WITHIN TWO DAYS; CASES DIVIDED ACCORDING TO THE DAY OF THE HEMORRHAGE ON WHICH THE TEST WAS MADE

Classification	Day of Hemorrhage	Number of Cases	Tests	—Clotting-Time in Minutes— Average	Longest	Shortest
Severe and light	1	6	7	6	8½	3⅜
Severe and light	2	2	2	6⅛	7⅜	4⅞
Severe and light	3	13	1	2¼	2¼	2¼
Severe and light	4	0	.	...	...	...
Severe and light	5 and after	4	5	5⅝	8	3⅜
Streaked	1	3	5	6	7¾	3⅞
Streaked	2	5	5	5½	7⅞	4
Streaked	3	2	2	5¾	6	5½
Streaked	4	1	2	3⅝	3⅜	3⅜
Streaked	5 and after	3	4	5¾	7⅜	4¼

TABLE 14.—HEMORRHAGES THAT WERE SEVERE OR SLIGHT AT FIRST DIVIDED ACCORDING TO WHETHER THEY WERE THE SAME WHEN THE TEST WAS MADE OR WHETHER THEY HAD DIMINISHED TO STREAKS

Condition at Time of Test	Number of Cases	Number of Tests	Clotting-Time in Minutes—Average	Clotting-Time in Minutes—Longest	Clotting-Time in Minutes—Shortest
Severe or slight.....	4	7	6½	8	3⅜
Streaked sputum	6	6	5¼	7⅜	2½

TABLE 15.—RECORDS ON THE SAME PATIENT TAKEN BOTH BEFORE AND DURING A HEMORRHAGE

Day before Hemorrhage	Clotting-time	Day of Hemorrhage	Clotting-time
5	7½	5	5¾
38	7½	3	2¼
36	6½	½	3⅞

TABLE 16.—HEMORRHAGE WITHIN SEVEN DAYS OF TEST BUT WHICH HAD CEASED WHEN TEST WAS MADE

Classification	—Number of— Cases	—Number of— Tests	——Clotting-time in Minutes—— Average	——Clotting-time in Minutes—— Highest	——Clotting-time in Minutes—— Lowest
All kinds	6	8	6⅓	10⅜	3⅝
Severe	2	3	5¾	7½	4½
Slight	3	3	7½	10⅜	5¼
Streaked	1	2	3⅝	3⅝	3⅝

G. Hemorrhage in Typhoid Fever: Wright believes that severe intestinal hemorrhage and hemorrhage from comparatively small wounds supervening in the course of typhoid fever are apparently associated with diminished coagulability. Chantemesse found the clotting-power of the blood in typhoid fever much lowered on the eve of a hemorrhage. Robertson, Illman, and Duncan noted that the coagulation-time was shortened following hemorrhage in typhoid on numerous occasions and lengthened just prior to hemorrhage in several cases. In one instance a hemorrhage of 15 ounces caused the coagulation-time to drop from eight minutes to three minutes and ten seconds; in another a decided hemorrhage of twenty-one ounces brought the clotting-time down from four minutes and a quarter to one minute and forty-five seconds. They observed that cases in which the clotting-time did not go above normal escaped such accidents as hemorrhage.

None of Hinman and Sladen's cases with hemorrhage had a delayed time, although all of them showed a shortened time after the hemorrhage.

Only one of the twelve typhoid fever patients I examined had a hemorrhage from the bowels, but in this one the clotting-time was the longest of all and a third longer than the average of the twelve. The average clotting-time of three cases having epistaxis was only a slight fraction shorter than the average time of the twelve, thus failing to bear out Wright's assertion that deficient coagulability exists in cases of epistaxis.

H. Hematuria: In a case of persistent hematuria due to heart and kidney disease the clotting-time estimated with both my method and Milian's was shortened markedly at one time, less later. The clotting-time on September 12 was four and three-eighths minutes; on September 19, four and three-eighths minutes; on September 23 seven minutes, and on September 26, seven minutes.

Addis also found the coagulation-time shortened in a patient with cancer of the bladder, who had had hematuria for three months.

I. Hemoglobinuria: In a patient with paroxysmal hemoglobinuria, examined when there had been no blood in the urine for five days, the clotting-time was slightly shortened—seven minutes with my coagulometer.

J. Hemorrhagic Diseases of the New-Born: Two cases of hemorrhagic disease of the new-born are reported by Schwarz and Ottenberg. The blood of the first was kept for four days and showed no sign of coagulation. The coagulation-time of the second also showed very marked delay; after five hours a few threads of fibrin had formed.

3. Hemophilia.—Hemophilia is the one disease universally believed to be characterized by a deficiency of coagulation. According to Wright there is also a notable leukopenia, especially polynuclear, hemophilic blood being deficient in the cellular elements which contribute the nucleo-albumin element in the formation of fibrin.

4. "Serous Hemorrhages."—Wright applies the term "serous hemorrhages" to increased transudation of plasma through the capillary wall, as seen in pleural effusion, serous diarrhea, etc., and suggests the existence in such cases of a connection with deficient blood-coagulability. Other examples are urticaria, chilblains, edema of the feet and hands not due to circulatory or kidney lesions, cyclic albuminuria, the lymphatic type of headache.

A. Effusions in Serous Cavities: Six patients with pleural effusion that I examined with Wright's tubes, had a shortened average clotting-time of only one and one-half minutes (five and one-fifth minutes in terms of my method), while one patient with hydropneumothorax, one with empyema, and one with pyopneumothorax, tested with my method, gave shortened coagulation-times of four and one-half, three and one-half, and three and three-eighths minutes, respectively. On the other hand, one case of pleural effusion in a tuberculous patient, investigated according to my method, had a lengthened clotting-time of over ten and one-eighth minutes, and three patients with ascites gave a normal average clotting-time of two and one-half minutes with Wright's tubes (eight and two-thirds minutes in terms of my method), with limits of three and one-quarter minutes and one minute (ten and three and one-third minutes in terms of my method). It would seem plausible that the reabsorption into

the blood of the serum from pleural effusion might sometimes have a tendency to shorten the clotting-time.

B. Serous Hemorrhages into the Intestinal Canal: Wright remarks that constipation is rare in hemophilia and that diarrhea is often coincident with a period of diminished coagulability. I found no lengthening of the clotting-time in cases of diarrhea. Four patients with diarrhea tested with Wright's coagulometer, had an average clotting-time of two and three-quarters minutes (four and one-third minutes in terms of my coagulometer), and in eleven cases of diarrhea complicating tuberculosis there was an average time of five and one-sixth minutes with my method.

C. Edema: A case of edema of the feet associated with polyuria had a normal clotting-time of eight minutes with my method. Five patients with edema that I examined with Wright's method gave an average normal clotting-time of two and one-half minutes (eight and two-thirds minutes in terms of my method), with limits of four minutes and one minute (twelve and one-third and three and one-third minutes in terms of my method). Addis obtained a normal coagulation-time in two cases of anasarca due to heart disease.

D. Urticaria: Wright thinks it probable that most urticarias are due to diminished coagulability, especially the form that supervenes on the administration of diphtheria antitoxin and on the consumption of acid fruits and vegetables. Hinman and Sladen found the clotting-time in urticaria variable, being in some cases lengthened to nine and one-half minutes. The time was normal in Addis' two cases. Of my two cases of urticaria one, which followed vaccination, had a slightly lengthened clotting-time of eight and seven-eighths minutes as tested with my coagulometer, while the other had a diminished clotting-time—five and a half minutes.

E. Chilblains: Wright believes chilblains to be associated with a condition of defective coagulability. This is not borne out by my case, examined with my coagulometer, which had a clotting-time of seven minutes.

F. Lymphatic Headache: The lymphatic type of headache, according to Ross, occurs frequently in women and occasionally in men. It is present and most severe on waking and tends to lessen in intensity or altogether disappear in one to six hours. It usually manifests itself as a dull heavy ache or as a frontal or temporal throbbing. Ross and Luff both state that lymphatic headache is associated with deficient coagulability of the blood.

G. Physiologic Albuminuria: Wright and Ross state that in physiologic albuminuria the renal function is entirely unimpaired. In many of their cases they found a condition of diminished blood coagulability.

H. Vasomotor Ataxia: I include vasomotor ataxia, described by Solomon Solis Cohen, under "serous hemorrhages," as the two syndromes present many features in common—angioneurotic edema, urticaria, headache, and physiologic albuminuria. I might state parenthetically that I regard Strümpell's "exudative diathesis" as practically identical with these syndromes, being distinguished by a tendency to exudative processes, as urticaria, intermittent swelling of the joints, angioneurotic edema, etc. One of my patients with vasomotor ataxia was subject to chilblains. My three subjects of vasomotor ataxia examined with my coagulometer had an average clotting-time of seven minutes, a little less than normal.

5. Anemia.—Vierordt, Hassel, Ehrlich and Lazarus, and Bezançon and Labbé found the coagulation-time of the blood shortened in anemia, but Wunderlich states that there are many exceptions to this rule. Wright states that the coagulability is diminished in chlorotic girls.

Weiss, on the contrary, reports unusually long coagulation-time in chlorosis and severe anemia.

Hinman and Sladen found no markedly delayed time in primary anemia or as a rule in secondary anemia, although in two very severe cases of the latter there were prolonged coagulation-times. A normal coagulation-time was observed by Addis in two cases of chlorosis and one case each of pernicious anemia and of secondary anemia. In one case of severe chlorosis the time was at first slightly lengthened, becoming normal as improvement set in. In a case of pernicious anemia the time was persistently short in spite of very great improvement in the blood condition.

In my twenty-three cases of anemia, as well as in the sixteen with a hemoglobin between 50 and 75 per cent., the clotting-time was normal, two and one-half minutes with Wright's tubes (eight and two-thirds minutes in terms of my method); in five cases with a hemoglobin below 50 per cent., the time was increased very slightly, being two and five-sevenths minutes, as tested with Wright's tubes (nine and six-fifteenths minutes in terms of my method).

6. Leukocythemia.—According to both Muir and Weiss the blood in leukocythemia coagulates less readily than normal blood. Addis' case of myelogenous leukemia had a shortened coagulation-time of five minutes, twenty-five seconds.

7. Jaundice.—An increase in the coagulation-time is generally believed to accompany jaundice. Robertson, Illman, and Duncan found the clotting-time increased in their cases. Hinman and Sladen, working with the Boggs instrument, obtained a normal coagulation-time of from five and a half to six minutes in cases of catarrhal jaundice, times ranging from five and a half to twelve and a half minutes in jaundice due to

cholelithiasis, and an average time of thirteen and a half minutes, with limits of nine and twenty and a half minutes, in jaundice due to malignant disease. In none, however, of Murphy and Gould's fifteen jaundice cases, the lesions of which embraced nearly every known cause of jaundice, did the coagulation-time vary from the normal. Vierordt, on the other hand, obtained a shortened clotting-time in jaundice.

Addis found normal coagulation-times in two cases of catarrhal jaundice and one case each of abscess of the liver, carcinoma of the liver, and cirrhosis of the liver, a slight prolongation of coagulation in a case of hepatic cirrhosis and a shortened time in a case of secondary hepatic carcinoma with very profound jaundice and hemorrhages. From a study of similar cases, Morawitz and Bierich believe that in many cases of jaundice, probably the greater number, the coagulation-time is normal and there is no tendency to bleeding. In cases of cholemia, in which an hemorrhage tendency exists, coagulation-time, they state, is markedly lengthened but not from the direct action of circulating bile salts. In my two cases of jaundice the clotting-time was increased, averaging eleven and one-eighth minutes, with my method.

8. Tuberculosis.—Anders regards as undoubted the existence of a hemorrhagic tendency in a considerable percentage of cases of pulmonary tuberculosis and believes that a veritable hemoptysis may be induced in such by increased pressure in the pulmonary circuit. Wright also speaks of a diminished coagulability in those subjects of phthisis in whom excessive hemorrhage occurs. In Addis' twelve cases of tuberculosis infections the coagulation-time was normal. Both Vierordt and I found the clotting-time shortened in pulmonary tuberculosis. Vierordt, using his apparatus, found the clotting-time to be three minutes in phthisis and five minutes in phthisis with cavity. About eight years ago, with Wright's tubes, I obtained an average clotting-time of two and one-quarter minutes (seven and four-fifths minutes in terms of my method), in four cases of pulmonary tuberculosis. More recently I investigated 100 cases of pulmonary tuberculosis, using my method. The average clotting-time was five and one-sixth minutes, the average time for the different stages varying very slightly from this.

TABLE 18.—CLOTTING-TIME IN PULMONARY TUBERCULOSIS

	All Stages	First Stage	Second Stage	Third Stage
Number of cases	100	26	27	47
No. observations	134	32	32	70
Aver. clotting-time (minutes)	5 1/6	5 1/7	5 1/7	5 1/5
Max. clotting-time (minutes)	10⅜	8½	8½	10⅜
Min. clotting-time (minutes)	2⅛	2⅛	2½	2⅝

The shortened coagulation-time may have been due to some factor other than the existence of tuberculosis. The patients were all drinking

large quantities of milk which, as will be shown later, is said to hasten coagulation through the calcium it contains. As a rule the tests were made out of doors or in a well-ventilated ward, exposing the blood to the air for the short space it was uncovered. Many of the tests were made in the late afternoon. Practically all the tests were made during the hot and humid summer months. In addition to the perspiration from this cause, some of the patients had the water content of their blood further depleted by night-sweats, while others perspired more than usual on account of cardiac weakness.

9. Typhoid Fever.—During the acute stage of typhoid fever a lengthened clotting-time has been noted by Wright, Hinman and Sladen, Robertson, Illman and Duncan, and Wright and Knapp. This agrees with my own records. Twelve tests made with Wright's tubes during the acute stage gave a clotting-time of two and seven-eighths minutes (ten minutes in terms of my method). In all of Addis' ten cases, on the other hand, the coagulation-time was shorter than normal during the acute stage. Vierordt obtained a shortened clotting-time in typhoid fever, but does not say in what stage of the disease.

The general lengthening of the coagulation-time in the acute stage of typhoid fever, Wright and Knapp compare to the lengthening of the clotting-time that supervenes on the inoculation of large doses of "anti-typhoid vaccine." This increased coagulation-time, they say, furnishes an explanation of the serious hemorrhages which may occur from comparatively small lesions in the typhoid intestines. Chantemesse found the coagulation-time of the blood in typhoid fever patients much increased on the eve of a hemorrhage.

In convalescence from typhoid fever Wright and Knapp observed a marked shortening of the clotting-time of the blood. In their first eight cases the clotting-time was on the average four and a half times shorter in the convalescent stages than during the course of the fever (four and a half minutes against twenty minutes). The coagulation of the blood was abnormally rapid in four cases, in each of which femoral thrombosis supervened—the only cases in which thrombosis occurred. These authors found the quantity of lime salts in the blood of typhoid convalescents greatly in excess of that in normal blood and suggest that the increased coagulability during convalescence may be dependent on an excess of lime salts. This excess of lime salts, they claim, must be obtained from the milk. Chantemesse also finds the coagulation-time becoming shorter in the late stage of typhoid fever when the complication of phlebitis tends to supervene. A practically normal clotting-time, on the other hand, was exhibited during convalescence by Hinman and Sladen's typhoid fever patients this time, which averaged seven minutes, some individual cases showing marked shortening. In the cases exhibiting thrombosis the

longest time was six and a half minutes, the average being five and a half minutes. The majority of their patients were on a milk-albumin diet, but the few fed more liberally showed no difference from the general group. In all but one of Addis's cases the coagulation-time, which had been shortened during the acute stage, returned to normal as convalescence set in, and there was no thrombosis. In the one case, however, the time remained short and thrombosis occurred.

The clotting-time of the blood of the typhoid patients of Robertson and his associates returned to normal during convalescence, but showed no decided inclination to become shorter than normal. These observers, however, are of the opinion that such inclination exists where phlebitis and thrombosis develop. Their patients were allowed a liberal diet, milk being given sparingly, in most cases not at all.

My experience agrees with that of Robertson and his associates. The average time of five tests made with Wright's tubes during convalescence was normal, being two and three-tenths minutes (eight minutes in terms of my method).

10. Acute Exanthemata.—Cabot and Ehrlich state that clotting is slow or fails to occur in the acute exanthemata.

11. Pneumonia.—Hayem, Pye-Smith, and Coleman found the clotting-time prolonged in pneumonia. Addis obtained a normal time in three cases of pneumococcal empyema infection, a slightly irregular time in one case, a time shorter than normal in another, and a time at first longer and afterwards shorter than normal in still another. My six pneumonia patients, tested with Wright's tubes, had a slightly shortened average time of two minutes (seven and one-half minutes in terms of my method).

12. Rheumatism.—Slight retardation of the coagulation-time was observed by Hayem in rheumatism and by Addis in three cases of severe rheumatic fever. The time was normal, however, in the latter's seven ordinary rheumatic cases. My three cases had a slightly shortened time of one and five-sixths minutes with Wright's tubes (six and three-fifths in terms of my method).

13. Appendicitis.—Coleman's observations, as far as they went, showed in appendicitis a coagulation-time longer than the normal average.

14. Carcinoma.—The coagulation-time was normal in Addis' six cases of carcinoma and in Denk and Hellman's twenty cases of malignant neoplasm without cachexia or wasting, but it was shortened in the latter's cases of cachexia from this disease and in Weiss' cases of cancer.

15. Chorea.—An unusually long clotting-time was exhibited by Weiss' cases of chorea.

16. Nephritis.—Addis obtained normal coagulation-time in a subacute case and in a fibroid case of nephritis, an abnormally short time

in one acute case and prolonged times in two acute cases and in one case of uremia. Weiss found the time prolonged in acute nephritis.

Three nephritic patients I examined with Wright's tubes gave a prolonged average clotting-time of three and one-quarter minutes (ten and two-thirds minutes in terms of my method), with limits of four and two and one-quarter minutes (thirteen and seven and one-half minutes respectively in terms of my method). On the other hand, three patients examined with my method gave a diminished average time of six and one-eighth minutes.

17. Eclampsia.—In eclampsia Weiss observed a prolonged clotting-time.

18. Scorbutus.—Weiss' cases of scurvy presented an unusually long coagulation-time.

19. Myxedema.—The coagulation-time was normal in Addis' case of myxedema but prolonged in Weiss' two cases.

20. Exophthalmic Goiter.—Several goiter patients examined by Weiss had an unusually long clotting-time, while Addis' case had a normal time.

21. Acromegaly.—Weiss found the time lengthened in three cases of acromegaly.

22. Tetany.—A prolonged time was observed by Weiss in tetany.

23. Diabetes.—Addis always observed a normal coagulation-time in his two cases of diabetes, despite the existence of pronounced lipemia and coma in one of them.

24. Pyogenic Infections.—In twelve patients with severe localized septic infection, examined by Addis, the time was normal, whereas coagulation was delayed in three cases of septicemia.

25. Skin Disease.—In acne, eczema, and furunculosis Weiss found the clotting-time unusually long.

26. Endocarditis.—Four patients with endocarditis that I tested with Wright's tubes had a shortened average clotting-time of one and one-quarter minutes (four and one-third minutes in terms of my method). In two patients examined with my method the shortening was not so marked, the times being five and three-quarters minutes and six minutes respectively.

27. Myocarditis.—In three cases of myocarditis I examined, the average coagulation-time with Wright's tubes was two and one-quarter minutes, practically normal (eight minutes in terms of my method).

28. Aneurysm.—I have measured the clotting-time in two cases of aneurysm. One patient, examined with Wright's tubes, had a markedly diminished time of one and one-quarter minutes (four and one-third minutes in terms of my method). Another patient, tested with my

method on ten different occasions over a period of three months, usually had a clotting-time below normal, the last taken before his death being the only delayed time. The times were: May 7, seven and one-half minutes; May 11, five and one-half minutes, May 18, seven and three-eighths minutes; May 22, six and one-quarter minutes; June 24, six and one-quarter minutes; July 8, seven and five-eighths minutes; July 16, eight and one-quarter minutes; July 22, six and one-half minutes; August 5, eight and one-quarter minutes; and August 19, ten and one-quarter minutes.

29. Epilepsy.—Turner has shown that as compared with that of persons in good health, the blood of epileptics coagulated in a shorter time, and also that this is more marked just before or during fits than when the patient is free from them. Speaking generally, he says the greater the frequency of fits in a case, the quicker is the average coagulation rate. The coagulation rate is quickened during and before attacks of *petit mal* as well as of *grand mal.*

From his point of view it is not essential—indeed it is highly improbable—that in every case a specially quick coagulation rate should correspond to the time of the fit; the reverse is more important—that the fit should coincide with a time of rapid coagulation. It does not follow that, because the tendency is increased, therefore coagulation must occur. In Turner's opinion it is in this connection that we have the means of harmonizing the thrombotic and the toxic theories of epilepsy, by attributing this idiosyncrasy of the blood to a toxin which, when it reaches a certain intensity, excites local coagulation.

Besta, on the other hand, out of forty-five epileptics found lengthened clotting-time in thirty-seven. A prolonged clotting-time in epilepsy was also observed by Weiss.

Silvestri holds the view that epilepsy is due to a diminished percentage of calcium salts in the blood. Coleman reports a case of hystero-epilepsy due, he says, to calcium deficiency, in whom the calcium index was 0.68 to 0.7 before menstruation and 0.1 when the menstrual flow commenced.

Clinical evidence seems to support both views. Good results are reported from the use in epilepsy of calcium salts, thyroid extract, and blood-serum, all of which are believed to shorten the clotting-time; while benefit in this disease has frequently been obtained from the administration of bromids, which are said to lengthen the clotting-time.

30. Dementia Præcox.—According to Perugia the coagulability of the blood is normal in maniacal and paranoidal dementia præcox but increased in the catatonic form.

31.—Thrombosis.—Wright states that intravascular thrombosis is indicative of an unduly high blood-coagulability, to which opinion Denk and Hellman apparently subscribe. In addition to this cause Chante-

messe adds two others, which he considers play very important rôles: a general, and especially a local slowing of the circulation, and the presence in the walls of the vein of microorganisms provoking the formation of a clot. Brooks and Crowell have shown, however, that experimentally none of these acts except in the presence of a lesion in the walls of a blood-vessel. Bernheim's work would seem to confirm this view. Addis found the coagulation-time normal in six cases of thrombosis. The time in my case was shortened, being five and five-eighths minutes.

V. FACTORS INTRODUCED INTO THE BODY FROM WITHOUT

The coagulability of the blood while within the vessels is influenced by many factors introduced into the body from without.

1. Calcium Salts.—The internal administration of one of the salts of calcium produced shortening of the clotting-time in the hands of Wright, Rogers, Luff, Chantemesse, Boggs, Kobert, Ross, Coleman, Carrière, Weil, Weiss, Hinman and Sladen, Wright and Paramore, Denk and Hellmann, Brooks and Crowell, and Simpson. That calcium salts have no effect on the clotting-time is asserted, on the other hand, by Addis, Labbé, Morawitz and Lossen, Dahlgren and Robertson, Illman and Duncan. The effect of the administration of calcium salts on the coagulation-time of healthy people appears, from Rudolf's experience, to be slight, or absent. No shortening of the clotting-time was observed after exhibition of calcium salts in those few of my patients whose blood was tested in this connection. Coe noted sometimes hastened coagulation and sometimes no change at all after giving that drug.

Wright and Paramore state that the full accelerating effect of calcium chlorid is achieved within the first hour after its administration, and of calcium lactate within twenty to forty-five minutes. This is confirmed by Weiss. Coleman believes, however, that calcium chlorid when administered by the mouth is absorbed slowly and incompletely. The clotting-time of the blood of two rabbits was not appreciably affected four hours after 0.5 gm. of calcium chlorid was given by the mouth, whereas 0.1 gm. given hypodermically shortened the coagulation-time very considerably within less than an hour from its administration.

Wright and Paramore believe that there are as between different individuals a conspicuous difference in their capacity of responding to calcium, which they referred to a constitutional difference in the matter of absorption of calcium chlorid.

The action of calcium salts seems to bear some relation to the dosage. Wright and Paramore gave single doses each of 60 grains of calcium chlorid or lactate. Wright states that while in small doses, or in large doses given for a short time, calcium hastens the clotting-time, the continued administration of large (20 to 30 grains) doses results in a second

diminution of coagulability to below normal. Bezançon and Labbé also state that if a certain quantity of a calcium salt is added, coagulation is accelerated, but if an excess of calcium is present (more than 2 to 100), the blood becomes equally incoagulable. Weiss also says the dose must not be too large, and recommends 30 to 45 grains a day in an adult for five or six days, stating that the action lasts for weeks. Carrière states that to maintain the cure in hemophilia calcium must not be discontinued; if it is suspended, the symptoms soon reappear. Labbé gives the caution that, taken in large doses or over a long time, calcium can lengthen the clotting-time instead of shortening it. According to Hinman and Sladen, however, when one continues calcium too long, the effect wears off and the time returns to about what it had been previously. They believe that calcium increases the coagulability, but can maintain it only about three to five days. If the dosage is then increased, the time is again shortened.

Bell and Hick think that there is a maximum amount of calcium in the blood with a quickest normal clotting-time, which cannot be increased by excess of calcium salts either administered orally or injected subcutaneously. They say that the apparently delayed clotting-time from the oral administration of an excess of calcium is not due to an excess but to a deficiency, it being probable that after excessive dosage the body becomes immune or resistant to the absorption of calcium salts, or excessively active in their excretion.

The purity of the preparation is considered by Simpson to be a very important factor, his attention having been called to some instances where the inferiority of the preparation has minimized the results.

2. Milk.—Seventeen observations made by Wright and Paramore showed that the coagulability of the blood is increased by the ingestion of milk, and that this increased coagulability is associated with the presence of large quantities of calcium and magnesium salts in the blood. They therefore regard milk as more than a foodstuff, as also in an eminent degree a medicinal agent. Denk and Hellmann also found a shortened clotting-time in nearly all of twenty-three patients on a milk diet.

Wright and Knapp suggest that the increased coagulability during convalescence from typhoid fever may be dependent on an excess of lime salts obtained from cow's milk, which contains 1 part in 600 of calcium oxid as compared with 1 part in 800 in lime-water. If the milk dietary is the key to the frequency of thrombosis, they regard it as probably the key to other problems, in particular the frequently beneficial effect of a milk dietary on "serous hemorrhage" from the kidney. They compare the rarity of thrombosis after acute fevers where a milk diet is not imposed. Robertson, Illman, and Duncan, however, obtained no shortening of the clotting-time from the administration of milk in cases showing

abnormally long times. Nor did it appear from Coleman's experiments that milk as a diet increased the coagulability of the blood.

3. Strontium Salts.—Nias states that strontium lactate in doses of 1 to 2 gm. is a serviceable substitute for the salts of calcium when the latter are not absorbed from the alimentary canal. He refers to a case of hemophilia in which calcium salts were not absorbed when administered by the mouth, but in which soluble salts of strontium when given by the mouth were absorbed with facility. He reduced the coagulation-time of his own and a patient's blood with 0.5 gm. to 2 gm. doses of strontium lactate.

4. Magnesium Salts.—Wright and Paramore on four occasions by the administration of magnesium carbonate caused the clotting-time to be accelerated in the ratio of 1 to 1/3 to 1 to 5/8. One patient was unaffected, the clotting-time remaining thirty-five seconds. In two observations the acceleration of the clotting-time was registered in one hour from the administration of the drug. There was distinct evidence in four cases of absorption of the magnesium salts into the blood.

Nias found magnesium lactate in 1 to 2 gm. doses a serviceable substitute for calcium salts when the latter were not absorbed from the alimentary canal, being able to reduce the clotting-time 30 per cent. in a case that was unaffected by calcium lactate. He regards the lactate of magnesium more rapid in its effects than the carbonate.

5. Citric Acid and the Citrates.—Wright, Bezançon and Labbé, Robertson, Illman and Duncan, Chantemesse, Hinman and Sladen, Coleman, Weiss, Rudolf, and Denk and Hellmann have found that the administration by mouth of citric acid and the citrates lengthens the clotting-time. It seems to Hinman and Sladen, however, that the effect wears off after from three to five days, necessitating an increase in the dosage if the lengthened time is to be maintained. According to Chantemesse, when totally obliterating phlebitis with great edema occurs in typhoid fever, the taking of a small dose of citric acid can prevent the phlebitis extending and the clot prolonging. But if the dose be a little too strong or prolonged, the clot dissolves too rapidly; it crumbles, and its particles, thrown into the general circulation, cause an intermittent febrile disturbance.

No lengthening at all of the clotting-time after the administration of citric acid was observed by Addis or Turner, a shortening being noted in two of the latter's three cases, who were having fits at the time. Rogers found that citric acid caused both lengthening and shortening of his own clotting-time.

6. Sodium Chlorid.—Blümel considers sodium chlorid the most reliable means at our command for controlling hemoptysis. Ten minutes after the ingestion of 10 gm. sodium chlorid by mouth the coagulation-

time was reduced from three and three-quarters to one and one-half minutes, and after another ten minutes to one minute. He gives it in dram doses in half a glass of water, repeating it if required at intervals of one and a half or three hours. Saline infusion, however, Blümel regards as contra-indicated.

Coleman has shown that solutions of normal saline injected subcutaneously have a pronounced effect in lengthening the coagulation-time of the blood.

7. *Blood-Serum.*—The injection of blood-serum subcutaneously in conditions in which there is a tendency to hemorrhage, with an increased coagulation-time, has been followed by shortening of the clotting-time according to Weil, Labbé, Schiffers, Busse, Carrière, Denk and Hellmann, and Beach.

Weil finds the serum of man, rabbits, horses and cattle equally efficacious, although *in vitro* the action of human serum is more evident. Both he and Leary state that beef serum is often toxic. The latter says that human serum is occasionally so. Wirth prefers horse's serum. Many employ diphtheria antitoxin. As a rule, fresh serum is employed. Weil and Labbé say it should not be more than two weeks old.

The dose is usually 15 c.c. when injected into a vein, or 30 c.c. when given subcutaneously.

The effect of the serum manifests itself at the end of forty-eight hours and lasts at least twenty-five days, being gone at the end of five weeks.

Serum has also a local hemostatic action, according to Weil, Labbé, Wirth, and Trembur.

It is a question in my mind whether the good effects reported by Crile and others from direct transfusion of blood may not in some cases have been due to this action of blood-serum in shortening the clotting-time, and whether the same results might not have been attained in some of those cases by the subcutaneous injection of blood-serum.

On the other hand, Bezançon and Labbé make the statement that the intravenous injection of blood or serum from a foreign species of animal retards coagulation. The injection of serum had no effect on the coagulation-time of the hemorrhages in Schwarz and Ottenberg's case of hemorrhagic disease of the new-born. Boggs noted lengthening of the clotting-time in rabbits following injection of dog's serum and of rabbit serum. Weil states that in excessive doses serum, instead of favoring coagulation, retards it.

Interesting in this connection is the action of blood-serum, usually in the form of diphtheria antitoxin, in causing profuse clotted menstrual flow, as reported by Collier, and in producing the so-called serum disease, accompanied by urticaria. Wright has shown that as the symptoms of serum disease develop there occurs a diminution in the coagulability of

the blood and both he and Netter treat and prevent serum disease by the internal administration of calcium salts which are believed to hasten coagulation.

Two years ago at a meeting of the Pennsylvania State Medical Society I suggested a possible existence in anaphylaxis of a condition similar to serum disease, with lengthening of the coagulation-time of the blood, on account of the prominence of urticaria as a symptom in many of the cases of sudden collapse following the injection of diphtheria antitoxin. Since then, Biedl and Kraus have found in dogs that a greatly decreased coagulability of the blood occurs in the anaphylactic state. Richet's experience, however, indicates that incoagulability of the blood is not at all constant in anaphylaxis. The peculiar susceptibility to this accident of persons subject to asthma, and the occurrence in anaphylaxis of angioneurotic edema, asthma, urticaria, profound peripheral vasodilatation, and a lengthened clotting-time, make me think there may be some association between this tendency to anaphylaxis and vasomotor ataxia and serous hemorrhage, which present at one time or another all of the above features.

Another interesting and apparently contradictory fact in this connection is the benefit in some cases of bronchial asthma reported from the therapeutic use of diphtheria antitoxin.

8. Transfusion.—In a case of hemorrhagic disease of the new-born, reported by Schwarz and Ottenberg, blood which failed to clot at all just before transfusion clotted in three and one-half minutes at the end of the transfusion. As a previous injection of horse-serum had no effect, there can be no doubt that in some cases direct infusion of blood has advantages not possessed by fresh serum.

Duke reports two cases in which transfusion stopped spontaneous hemorrhages and one that was unaffected by it. The bleeding-time was markedly shortened in all, but the coagulation-time was practically the same before and after transfusion. Other cases of this same disease have been reported, in which the bleeding was instantly checked by transfusion, but in which the clotting-time has not been taken.

Coleman has shown that solutions of normal saline injected subcutaneously have a pronounced effect in lengthening the coagulation-time of the blood owing, he thinks, to its rapid absorption.

9. Extracts of Organs.—Bezançon and Labbé state that acceleration of coagulation is produced by the intravascular injection of nucleoproteids and organic extracts containing nucleo-albumins. As a local application to bleeding surfaces in cases of hemophilia, Wright employs a solution of nucleo-albumins, in the form of glandular extracts. He regards hemophilic blood as deficient in the cellular elements which contribute the

nucleo-albumin element to the formation of fibrin, and believes that the addition of nucleo-albumin is essential to the formation of a sound clot.

Following the works of Sahli, and Weil, Nolf, working with extract of spleen, and Morawitz and Lossen, employing kidney extract, conclude that extracts of organs correct a blood vice in hemophilia. The former, moreover, attributes the incoagulability of hemophilic blood to want of thrombokinase, the latter to a lack of balance among the normal colloids in the blood. Weil and Boyé, who recently took up this study anew, using the extracts of many organs on nine cases of hemophilia, concluded from their combined experiments that the extracts of organs do not each act in the same manner on the blood of hemophilics, some causing a constant retardation of coagulation, others acting in the opposite manner. The doses of extract and the animals from which they were produced seemed to be of little import. It seems more than probable to Bell and Hick that the ductless glands preserve a balance in the calcium metabolism—as they do in many other metabolic processes—one acting anabolically, another catabolically. Marchadier is of the opinion, however, that the action of organic extracts in hindering coagulation may be due to the alcohol they contain.

Owing to the difference, just noted, in the effect of extracts of different organs, these will be considered separately.

A. Thyroid Extract: Taylor states that normal blood, having the proper amount of coagulant element, is not affected by thyroid extract, even when the latter is continued for a long time and when it has to be discontinued on account of its pronounced constitutional effects. Thyroid extract seems to him to act only on blood lacking fibrin ferment. When the latter is markedly diminished, thyroid extract supplies it, according to Taylor, either by a direct action on the blood or, as Sajous thinks, by stimulating the anterior pituitary body, which excites the adrenals to greater activity, and thus increases the proportion of fibrin ferment in the blood. Taylor reports cases in which thyroid extract, given in 3-grain doses thrice daily, shortened the coagulation-time from eleven and one-half minutes to three minutes, four seconds, and from twelve and one-half minutes to six and one-half minutes, and mentions the cases of marked clinical improvement. Carrière, on the other hand, states that thyroid extract scarcely modifies the coagulability of the blood, while Weil and Boyé include thyroid extract with those extracts of organs that cause a constant retardation of coagulation.

B. Thymus Gland: Thymus gland in Wright's hands caused a shortening of the clotting-time and is used in his solution of cell nucleo-albumins. According to Carrière and Weil and Boyé, however, thymus gland extract almost always causes a slowing of coagulation. Boggs' results

with its use are at variance. It shortened the clotting-time in one rabbit and in others lengthened the time and made the blood incoagulable.

C. Pituitary Gland: According to Weil and Boyé the anterior and posterior lobes of the hypophysis have different and antagonistic actions on the clotting-time of the blood. Extracts of the former retard slightly, if at all, the coagulation of the blood in normal rabbits but retard coagulation in normal man in a constant and marked manner, acting similarly but less constantly toward the blood of hemophilics, which they render more incoagulable. Extracts of the posterior lobe invariably accelerate the coagulation of the blood in normal rabbits, and nearly always accelerate the coagulation of the blood in a normal man, also correcting in a nearly perfect manner incoagulable hemophilic blood.

D. Liver: Doyon and his associates have made careful studies of the relation the liver and bile bear to the coagulation-time. They believe that fibrinogen has its origin in the liver, the albumin of which they regard as the mother substance of fibrinogen. This, they think, explains the diminution of the coagulability of the blood that occurs in affections of the liver. Obliterating the arteries of the liver with paraffin usually brought about incoagulability of the blood. Total extirpation of the liver in the frog prevents coagulation of the blood. These authors have also shown that bile causes incoagulability of the blood through the intermediary of the liver. An injection of bile prevents clotting of the circulating blood in both rabbits and dogs, being more effective if made into the mesenteric veins. The incoagulability manifests itself the first minute following the injection and lasts from a very short time to several hours. These observations are confirmed by Kauders. Delezenne demonstrated that by causing peptone, eel-serum, or extract of crayfish muscle to circulate through the liver of a dog, a liquid is obtained capable of preventing the coagulation of the blood *in vitro* and of rendering the blood of a rabbit incoagulable.

Weil and Boyé found that liver extract caused constant retardation of coagulation. In both Carrière's and Labbé's hands, however, liver extract hastened the coagulation in some cases of hemophilia. In Boggs' different tests liver extract lengthened or shortened the clotting-time in dogs or rendered the blood incoagulable.

E. Gastro-Intestinal Extract: A piece of the gastric mucous membrane formed part of Wright's solution of nucleo-albumins.

Czubalski regards intestinal extract as identical with Witte's peptone in its quantitative relations.

Extracts of stomach and duodenum caused constant retardation of coagulation in Weil and Boyé's cases.

F. Kidney Extract: Kidney extract shortens the clotting-time, according to Morawitz and Lossen and Weil and Boyé.

G. Ovarian Extract: Weil and Boyé found that ovarian extract shortens the clotting-time. Grant reports a case of severe and grave traumatic hemorrhage cured by its use.

H. Testicular Extract: Extract of testicle is said by Weil and Boyé to shorten the clotting-time. In addition to the glands mentioned, testicular extract forms part of Wright's solution of nucleo-albumin.

I. Extracts of Spleen, Pancreas and Suprarenals: Weil and Boyé found that extracts of the spleen, pancreas and suprarenals caused coagulation to be constantly retarded.

10. Alcohol.—Alcohol lengthens the clotting-time of the blood, according to Vierordt, Wright, Rogers, Bezançon and Labbé, and Marchadier. In my cases, however, it did not seem to have any effect at all on the clotting-time. Of twenty-three observations made with Wright's tubes on twelve patients who were taking whisky, the average clotting-time was two and one-half minutes (eight and two-thirds minutes in terms of my method), the maximum being five and three-quarters minutes (nine and one-quarter minutes in terms of my method), and the minimum one and one-quarter minutes (four and one-third minutes in terms of my method).

11. Carbon Dioxid.—According to Wright, inhalations of carbon dioxid in the presence of sufficient oxygen shortens the clotting-time of the blood. Its local effect will stay epistaxis. Wright usually administers the gas through a tube, but he states that rapid respiratory movements will increase the carbon dioxid in the blood and hasten coagulation. He remarks, however, that asphyxia is not only unnecessary, but harmful.

Bezançon and Labbé state that saturation of the blood with carbon dioxid, as in asphyxia, renders it incoagulable.

12. Narcotics.—Doyon states that chloroform in certain doses causes incoagulability of the blood and coincidently produces grave hepatic lesions. It acts not directly on the blood, but by altering the liver, which Doyon believes to be the organ that secretes fibrinogen.

Hartman found that neither injections of morphin and scopolamin nor injections of lumbar anesthetics, such as novocain, had any effect at all on the clotting-time.

13. Leech Extract.—Injection of extract of the heads of leeches into the veins is well known to hinder coagulation.

14. Witte's Peptone.—It is also a matter of general knowledge that the intravenous injection of Witte's peptone renders the blood incoagulable.

15. Gelatin.—Carrière, Dastre and Floresco, and Kaposi state that gelatin has an accelerating action on the clotting-time of the blood, the results, according to Carrière, being less constant than with calcium. Bezançon and Labbé, however, say that this action remains to be proved,

while Labbé and Frain, Labbé, Brat and Landman say that gelatin does not shorten the clotting-time, Brat asserting that it even lengthens it.

Gley and Richard say that decalcified or neutralized gelatin does not possess the property of hastening the coagulation of the blood, but in some cases has even the opposite effect. The coagulating action of gelatin, they say, is not a property of that substance but is derived from its acid function and from the calcium it contains. Kobert also questions whether the action of gelatin is not due in large measure to the calcium it contains.

16. Colchicin.—Coleman obtained a very considerable lengthening of the coagulation-time following the hypodermic injection of colchicin into rabbits.

17. Nuclein.—Nuclein caused lengthening of the clotting-time in Coleman's rabbits.

18. Beta-naphthylamin.—Beta-naphthylamin caused lengthening of the coagulation-time in two of the three rabbits Coleman injected.

19. Zymoplasma.—Von Manteuffel and others have seen the clotting-time reduced by Schmidt's zymoplasma.

20. Persalts of Iron.—Rogers found the clotting-time of his blood markedly shortened after taking the persalts of iron.

21. Hydragogues.—Wright states that the administration of hydragogues shortens the clotting-time.

22. Atropin.—Gley found that atropin, as a rule, caused complete incoagulability of the blood, though in some animals the coagulation was merely retarded. Doyon and his associates have studied the effects of atropin on the clotting-time, finding that it regularly produces incoagulability of the blood which, however, does not result in a modification in the blood's content of fibrinogen.

23. Bromids.—Turner has noticed a retarding effect on the coagulation of the blood from the administration of potassium bromid.

24. Phosphorus.—Doyon, Morel and Kareff have shown that incoagulability of the blood follows subacute poisoning by phosphorus, and is produced by the accompanying hepatic lesion.

25. Diphtheria Toxin.—According to Coleman, diphtheria toxin increases the coagulation-time of the blood.

26. Curare.—Doyon states that in certain conditions curare causes incoagulability of the circulating blood, which may last several hours. He suggests as a possible explanation the presence of poisons in the complex mixture sold under the name of curare.

CONCLUSIONS

1. The coagulation-time of the blood is affected by extrinsic factors acting on shed blood and by intrinsic factors acting on the blood while it is still in the vessels.

2. The coagulation-time of the blood is shortened by contact with a foreign body and with dirt, by the withdrawal of a large quantity of blood, by mechanical disturbance of the drop, by evaporation, by heat, and when the drop is shallow. It is lengthened by cold. The clotting-time ordinarily is not affected by the size of the drop, but is apparently influenced by the end-point adopted, the personal equation, and by unrecognized sources of error.

3. Methods for measuring the coagulation-time vary in the sources of error they avoid or introduce. The most accurate method is Addis' modification of Brodie and Russell's method, which, however, is too intricate and cumbersome for general use. Milian's is the simplest method. My modification of Milian's method combines simplicity with accuracy and, in my opinion, is the best available method. It presents a contact surface limited in extent, clean, and uniform in character, maintains a fairly definite and constant temperature, prevents evaporation, provides for drops of uniform size, largely eliminates the personal equation, and presents fairly constant results.

4. The coagulation-time of the blood is shortened by contact with the tissues, with the wound, blood, lymph, and skin, and by continuation of the bleeding. It is unaffected by the part punctured, the depth and character of the wound, or by the character of the blood flow.

5. The coagulation-time of the blood in the vessels is unaffected by the outside temperature, the amount of sunshine, by blood-pressure, the amount of hemoglobin, the number of leukocytes, or the bleeding-time, by age, sex, time of day, menstruation, pregnancy, or the puerperium; it seems to be shortened by low barometric pressure, by restriction of fluids, and by exercise; it is apparently lengthened by increased viscosity, and by the taking of food.

6. The coagulation-time of the blood in the vessels is unchanged in the presence of fever, menorrhagia, metrorrhagia, slight hemoptysis, diarrhea, edema, vasomotor ataxia, moderate anemia, carcinoma, diabetes, localized pyogenic infections, myocarditis, and maniacal and paranoidal dementia præcox; it is shortened in the presence of traumatic hemorrhage, hemorrhage from a uterine carcinoma, severe pulmonary hemorrhage, hematuria, hemoglobinuria, endocarditis, dementia præcox, aneurysm and thrombosis; it is lengthened in hemorrhage from a uterine fibroid, in the acute stage of typhoid fever, in hemorrhagic disease of the new-born, hemophilia, lymphatic headache, physiologic albuminuria, the acute exanthemata, and possibly in chorea, eclampsia, scorbutus, acromegaly, tetany, acne, eczema, and furunculosis; it is apparently variable in effusions in serous cavities, urticaria, chilblains, severe anemia, leukocythemia, jaundice, tuberculosis, convalescence from typhoid fever, pneu-

monia, rheumatism, nephritis, myxedema, exophthalmic goiter, and epilepsy.

7. The coagulation-time of the blood within the vessels is shortened by strontium lactate, magnesium carbonate, blood transfusion, extract of the posterior lobe of the pituitary gland, kidney extract, ovarian extract, testicular extract, zymoplasma, and possibly by persalts of iron and hydragogues; it is lengthened by citric acid and the citrates, extract of the anterior lobe of the pituitary gland, liver extract, gastro-intestinal extract, extract of spleen, extract of pancreas, extract of suprarenals, chloroform in certain doses, leech extract, Witte's peptone, and possibly colchicin, nuclein, beta-naphthylamin, atropin, bromids, phosphorus and curare. No constant effect on the coagulation-time of the blood has followed the introduction into the body of calcium salts, milk, sodium chlorid, blood-serum, thyroid extract, extract of thymus gland, alcohol, carbon dioxid, and gelatin.

The absence of uniformity in the results obtained with several of the last group of substances may be in part due to the fact that they have been investigated by a large number of observers, which increases the opportunities for error.

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TUMORS OF THE PINEAL BODY

WITH AN ACCOUNT OF THE PINEAL SYNDROME, THE REPORT OF A CASE OF TERATOMA OF THE PINEAL AND ABSTRACTS OF ALL PREVIOUSLY RECORDED CASES OF PINEAL TUMORS

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Tumors of the pineal body are rare, and their symptoms often vague. Like hypophyseal tumors, pineal (or epiphyseal) tumors, may give the general symptoms of brain tumor, with certain focal signs, and in addition, by interfering with physiological function, may bring about distinct and characteristic disturbances in nutrition. When these two separate and distinct classes of symptoms, namely, the neurological and metabolic, are present, the diagnosis becomes reasonably certain and operative removal becomes a possibility.

The pineal body arises from a diverticulum of the roof of the third ventricle. As seen in the 3 to 4 months' embryo, it is a pear-shaped body, which in section shows a number of radiating compartments (lobuli), containing the parenchyma of the gland, irregularly separated by connective-tissue and vessels, which sink in from a connective-tissue capsule.

Its connections with the rest of the mid-brain are extremely difficult to trace out, especially the rudimentary prolongation of the tænia thalami, which possibly has to do with an early optic relationship.

Its embryonal character accounts for its being the site of teratomata.

The interior of the gland contains neuroglia cells, round or oval ganglion cells, and parenchyma. Marburg has found a structure which he considers to be a vestige of the parietal nerve represented in saurians. Cajal has described nerve fibers similar to sympathetic fibers. Ependyma cells are numerous in the gland. In the interior of the gland they are cubical, but gradually change as one proceeds toward the habenulæ, or the *"Schaltstück,"* to the posterior commissure. Here cylindrical or goblet cells are found. In the interior of the compartments there are few glia nuclei. The majority of the cells are small and polygonal, and the plasma stains very slightly. The nuclei vary from light to dark, and contain small and large granules. Cyst formations are found frequently at the base where the glia is thickest.

After the seventh year the normal pineal undergoes a process of involution. The tænia habenulæ consist almost entirely of sand. The connective tissue cells lose their form and nuclei and undergo hyaline degeneration. The ganglion cells disappear, the glia cells persist, and the

division between the lobes is lost, the connective tissue is increased. The glia prolongations become much more frequent, calcium salts appear in the hyaline portions (corpora arenacea) and the cysts enlarge and are more numerous. Some are apparently lined with ependyma (ependyma cysts). These dilated cysts were noted by Virchow, who spoke of them as hydrops cysticus glandulæ pinealis.

As for the glandular cells, they become more vacuolated, the nuclei more prominent and pigmented.

In the involution process, the ependyma cysts may become enlarged.

Little is known of the physiology of the pineal body in man. Phylogenetically considered, it seems to be in part a rudiment of a third (parietal) eye, which is found at the present time practically only in one Australian lizard (*Hatteria punctata*). Its anatomical connections with the optic paths argues for its having been at one time a light-perceiving organ. Cajal doubts this, however, and asserts that this body is one of the many blood glands of the body.

Injections of the gland substance by von Cyon brought about irregular alterations in the force and frequency of the heart-beat, chiefly slowing it. Von Cyon also found that injections of salts, similar to the pineal sand salts, produced analogous results. This investigator has drawn the conclusion that certain substances in the pineal serve as fixatives for certain salts which have some relationship to the activities of the hypophysis, either causing these salts to be utilized by other structures, or causing them to be laid down as concretions, pineal sand, etc.

Further, electrical stimulation of the pineal, in herbivorous animals, causes a contraction of the sac-like body with movement in the cerebrospinal fluid of the third ventricle. It thus may be regarded as regulating in some measure the pressure of fluid in the third ventricle. As it is a mooted question, however, whether the pineal body in man normally contains any muscular fibers, its influence on the fluid in the third ventricle is entirely speculative.

Finally, the glandular tissue in the pineal undoubtedly exercises some influence on nutrition. The histological evidence points to the facts that this structure contains elements which ally it to the blood-glands — the chromaffin system — and that like other members of this series, the hypophysis, thymus, thyroid, adrenals, etc., it plays a part in trophism. It forms one of the links in the interacting chain of this system, and a disturbance in its functions throws the combination equilibrium somewhat out of balance.

We have seen, however, that a marked involution of the gland takes place at the time of puberty, and hence if trophic disturbances are to be referred to this structure they probably are confined to childhood. We shall return to the interdependent relations of the pineal and others of

the series, especially of the hypophysis, in that portion of our paper dealing with the interpretation of the trophic symptoms found in pineal tumors.

The accompanying section (Fig. 1) may serve to recall that the pineal gland lies just beneath the splenium of the corpus callosum, being separated from it by the velum interpositum. It lies on the anterior corpora quadrigemina, from which it is also separated by a layer of pia mater, usually derived from the velum interpositum. Normally it is not more

Fig. 1.—Section of brain showing situation of pineal body, especially in relation to the aqueduct and corpora quadrigemina.

than one-third to one-half an inch in length, and is attached to the midbrain on either side. It forms, in part, a roof to the third ventricle posteriorly. The free edge of the tentorium of the cerebellum lies below and behind. The deep cerebral veins run in the velum interpositum, and, just about the tip of the gland, unite to form the large cerebral vein of Galen, which passes out of the brain at the great transverse fissure, below the posterior extremity of the corpus callosum and the corpora quadri-

gemina, to enter the straight sinus. The position of the aqueduct of Sylvius is especially to be noted in relation to hydrocephalus. Laterally, at the base, the optic thalami are in close proximity.

It thus lies close to the communications between the third and fourth ventricles, to the cerebellar and pontine spaces, and is in direct contact with the large venous channels that drain the central region of the brain.

Hence, in enlargements of the pineal, circulatory disturbances will develop first, with the formation of varying degrees of hydrocephalus. Often the hydrops develops with great rapidity, though it may do so very slowly, and is undoubtedly conditioned by at least two independent factors, namely, pressure on the veins of Galen, and obstruction to the aqueduct of Sylvius. Then again, there are reasons for believing that growths in this region further stimulate the production of cerebrospinal fluid, in which case an additional factor for hydrocephalus development comes into consideration.

SYMPTOMS OF PINEAL TUMOR

I. NEUROLOGICAL SYMPTOMS

Symptoms of increased intracranial pressure, due to the hydrocephalus, are always present, and are among the first noted. The majority of the cases show what seems to be a fairly rapid development in symptomatology, although this particular brain area will tolerate growths up to a certain size without many signs. As soon as the growth gets beyond this — usually described as walnut size — the symptoms augment, and bring about death rapidly.

Headache is usually the first symptom, sometimes preceding the others by six months or a year, at other times appearing only a month or so before the fatal termination. The headaches vary, being mostly occipital, although they have been referred to a number of positions. They usually become diffused finally. They have the general characteristics of brain-tumor headaches, and, like them, show variations in intensity. Neuralgic, shooting pains also occur. Severe exacerbations are accompanied by attacks of vomiting and giddiness. Sometimes if the head be held in a definite position relief can be obtained. This is to be correlated with Weisenburg's remarkable case of movable tumor of the third ventricle.[1]

Papillary edema soon develops, and some of the patients have applied for relief on account of failing eyesight. The grade of the papillitis has varied greatly, but half of the patients have become blind.

Abnormal drowsiness or sleepiness has been characteristic in many, even in the early stages. It is probably a symptom of increased intracranial pressure, and furnishes, we believe, another proof that local pressure in the third ventricle, acting on the thalami, may be a cause of drowsiness, as well as increased pressure in the lateral ventricles acting on the cortex.

1. Weisenburg, T. H.: Brain, 1910, xxxiii, 236.

The hydrocephalus alone may later give rise to such motor phenomena as increased muscular tonus, weakness without paralysis of the extremities (principally the lower), increased tendon reflexes, even ankle-clonus and Babinski's sign. Isolated spacities due to hydrocephalus are the exception rather than the rule in pineal tumors. Almost invariably when the tumor has reached a sufficient size, or when it lies in such a position as to block off the aqueduct, pressure on the contiguous structures — corpora quadrigemina, floor of the aqueduct, superior cerebellar peduncles, etc. — introduces very significant neurological signs other than those due to the hydrocephalus.

Pressure on the corpora quadrigemina is almost inevitable, so that some ocular and pupillary signs, similar to those of third ventricle and corpora quadrigeminal tumors, are characteristic and constant. Isolated eye palsies occur with great frequency, and occasionally are very early signs. Nystagmoid movements, or nystagmus is not infrequent. Paralysis of associated movements, indicating pressure on the coordinating mechanisms in the posterior longitudinal bundles, are frequent and occur in varying combinations.

Of these, conjugate palsies, those for upward movements, have been noted with special frequency. This is in conformity with the widely accepted teaching that the nuclei for the superior recti muscles lie anteriorly in the general oculomotor grouping. Tsuchida controverts this anatomical teaching. Not all of the cases reported, however, have been well enough studied to draw positive conclusions. Partial skew deviations occur, the Magendie-Hertwig syndrome being among them.

Pupillary disturbances, also significant, are probably due, not only to the optic nerve changes, but also to pressure on the coordinating pupillary paths in the superior decussation of the anterior corpora quadrigemina, and also possibly to pressure on the posterior commissure, which is made up of the axis cylinders of the mesencephalic axone of the reflex oculomotor path. The pupils are usually widely dilated; they are frequently unequal, and are sluggish to light and in accommodation. One case is on record of dilatation of one pupil and contraction of the opposite one.

Facial palsies, slight and usually unilateral, have been observed. These are difficult to correlate.

Occasionally the tumor has pressed as far laterally as the geniculate bodies, and the posterior corpora quadrigemina on one or both sides. This probably accounts for the auditory symptoms, consisting of buzzing or crackling in the ear, or distinctly advancing deafness.

The superior cerebellar peduncles have also been involved in the direct pressure of these tumors with the causation of a series of interesting cerebellar signs. These have led to the false diagnosis of cerebellar growths. It should also be recalled that internal hydrocephalus apart from tumors can cause these symptoms.

Giddiness and dizziness have been constant, sometimes appearing very early. Staggering gait has been an early sign in nearly one-half of the patients; this has been the typical cerebellar gait, with marked pulsions; sometimes lateropulsion or retropulsion tendencies have preceded the development of the characteristic gait. Barany tests in one case (Bailey and Jelliffe) have shown implication of the vestibular paths, presumably in their mid-brain course.

Cerebellar asynergia and adiadokochinesis are comparatively recently described signs, and have been noted in the more recently reported cases (Marburg, Bailey and Jelliffe).

Ataxia, unilateral or bilateral in both extremities, but more particularly in the upper, is present in many cases. Occasionally only a tremor is noted.

Less constantly the symptoms of excessive thirst, polydipsia, with polyuria, have been recorded. These probably are symptoms due to still more remote pressure on the fourth ventricle, and properly should not stand in the foreground of the picture.

Glycosuria has been noted in a number of cases.

II. METABOLIC SYMPTOMS

To Marburg is due the credit of bringing into view a series of anomalies of metabolism, noticeably adiposis, associated with tumors of the pineal bodies. In a thorough discussion of the subject, he has called attention to the possible interrelations of the functions of the pineal and those of the pituitary bodies. Such relationship has been recorded before, but Marburg was the first to show that injury to the pineal might disturb metabolism. It has not yet been definitely established, but it seems probable for certain growths, particularly teratomata, that Marburg's contention is correct.

The symptoms which may come from pineal injury are, (a) adiposis, (b) early sexual maturity, and (c) cachexia.

A. ADIPOSIS

This has been recorded in a number of cases of pineal tumor. The increase in fatty tissue is apparently independent of the nature of the tumor, as it has not been confined to teratomata as Marburg originally thought, and as has been unduly emphasized by Frankl-Hochwart. It was present in our case to a definite degree. Schmidt's case of tumor (1837), not mentioned by Marburg, is recorded as "in exceedingly good state of nourishment"— *üppig*. Other cases are those of Nothnagel, Müller, Daly, Kny, Marburg, Frankl-Hochwart, and, less certain those of König, Falkson, Coats, Oestreich and Schlawky, Hempel, and Joukovsky.

Disease of the hypophysis also causes adiposis and consequently it is difficult to determine in many cases whether the pineal or the pituitary is at fault as there is almost invariably present marked third ventricle hydrocephalus. Pressure is extended to the infundibulum, and therefore on the hypophysis. In some of the cases the hypophysis has been much compressed, but in other cases — particularly in one reported on by Marburg — this structure has been normal. An appeal to statistics, however, cannot be made, since no notes have been made on the structure of the hypophysis in a number of the cases reported.

Fröhlich[2] and Erdheim[3] first brought into prominence the fact that adiposis might be due to hypophysis disturbance, and following them it has been established that definite metabolic syndromes are connected with increased and diminished functional activity of this structure. It is certain that (1) *hyperpituitarism* is associated with acromegaly, polyuria, and glycosuria, when the hypophysis is the site of a specific tumor — an adenoma (Benda[4]); (2) *hypopituitarism* is associated with adiposis, and disturbances in the organs of generation (dystrophia adiposogenitalis, Fröhlich), and that (3) *apituitarism* is associated with cachexia and grave trophic disturbances throughout the body, usually leading to death.

As far as the adiposis is concerned, it is certain that hypopituitarism is the usual condition that brings it about. Aschner's[5] experiments on dogs, in which he was able to keep the animals alive for from eight days to nine months, resulted in a definite retardation of growth, hypoplasia of the genitals, shortening of the skull, adiposis and apathy. These results are quite analogous to those found in man, when the hypophyses become atrophied or destroyed.

Whereas Fröhlich originally thought that the adiposis was due to a tumor of the hypophysis, and Erdheim maintained that it resulted not alone from such but from any new growth that encroached on the hypophysis, and stimulated an unknown center which he placed in the infundibular portion, it seems fairly well established that the adiposis is related to an injury or a destruction of the posterior lobe, and the infundibular portion of the hypophysis. Fischer's[6] recent summary presents the evidence, and reconciles many conflicting views of the previous investigators.

The chief obstacle to differential physiological diagnosis is the internal hydrocephalus. This is usually very marked in the third ventricle, and the infundibulum may be swollen and puffed out like a cyst, a condition

2. Fröhlich: Wien. klin. Rundschau, 1901, 47, 48.
3. Erdheim: Wien. Akad. Sitzsb., 1904, cxiii, abt. III.
4. Benda: Deutsch. klin., 1903.
5. Aschner: München. med. Wchnschr., 1909, lvi, 2668.
6. Fischer, B.: Hypophysis, Akromegalie und Fettsucht, Wiesbaden, Bergmann, 1910.

well seen in Knoblauch's case of glioma of the third ventricle. The swollen infundibulum can be seen also in our case. Such a hydrocephalus can unquestionably lead to adiposis. Nothnagel's early quadrigeminal case is to be thus interpreted. Müller's, Knoblauch's and Fischer's cases of dystrophia adiposogenitalis were due apparently solely to infundibular swelling with pressure on the hypophysis, although in these cases the hypophysis has not always been normal, as was that of Marburg. Fischer[8] calls attention to the fact that whereas in Marburg's case the hypophysis was reported as normal, yet there was "infundibular hydrocephalus."

The whole situation is in need of more extended study to determine whether pineal tumors alone can produce adiposis, apart from third ventricle hydrocephalus.

The anatomical situation of the hypophysis and its complicated histology render it difficult to correlate the mechanical and the histological features. Whether small or large amounts of pressure on the infundibulum or the pars intermedia, or the posterior lobe, or on the peduncles, will cause hyperactivity or hypo-activity cannot as yet be determined, nor can it yet be said what the actual state of functioning of the pars nervosa may be under varying conditions of pressure of hydrocephalus of the third ventricle.

The situation at present seems to be that adiposis is a frequent sign of hypopituitarism, and has been found as a result of a number of disturbances due to tumors of the pars nervosa of the pituitary, to tumors of the anterior lobes, to tumors in the region of the pituitary, to a bullet lodging in the pituitary, and finally, and most pertinent to this inquiry, to marked internal hydrocephalus of the third ventricle due to general causes of hydrocephalus, such as compression of the aqueduct by cerebellar tumors, by quadrigeminal tumors, by pineal tumors, and by tumors of the third ventricle.

In concluding this question we may say that there is some evidence to the effect that pineal tumors may cause adiposis, either through the disturbed function of that body, or else by acting on the hypophysis by means of hydrocephalus.

B. SEXUAL SPHERE

Next in importance to the increased fatty growth is the early development of the sexual characters. Gutzeit in 1896 called attention to this, and since this time the observations of Huebner, Frankl-Hochwart and Ogle have brought additional evidence. This early sexual development has shown itself as an enlargement of the penis, increase in the genital hair, or general hairiness of the body, increased libido, usually manifested by early masturbation, and, in some cases, changes in the voice.

Our own patient showed no changes in the organs, but the voice had changed. It was, however, high-pitched rather than deep. There were

some silky hairs on the boy's chin, though the general impression gained was one of feminism.

In other cases the menses have been interfered with. In Schmidt's case, already alluded to, menstruation had ceased at the age of 22. Conception had taken place at 15.

The interpretation of these changes in the sexual sphere is as difficult as that of adiposis. In the typical examples of dystrophia adiposogenitalis there is a lack of sexual development, and in some of the case histories this general syndrome of hypopituitarism is evident, but in others, and chiefly in those referred to, notably in children, sexual hypertrophy rather than atrophy is in evidence. Thus contradictions appear. If diminished hypophysis functioning is to account for the adiposis, this will not account for the increase in sexual precocity.

Possibly here the type of tumor introduces new elements that must be reckoned with, and whereas adiposis may be a more general factor dependent on hypopinealism, or on hydrocephalus, the sexual precocity may be due to the specific type of tumor, namely to teratomata, or possibly also to adenomata.

An analogous situation in the hypophysis has been noted by Fischer,[6] in which instance an adenoma caused an acromegaly with adiposis — a combination of hyper- and hypopituitarism.

Thus Oestreich and Slavyk are inclined to regard the early sexual ripening as analogous to an acromegaly (hyperpinealism). Further, Askanazy suggests that teratomata may be regarded as "false conceptions," in which one might expect, primarily at least, an increase in the pineal secretory functions.

Viewed from the point of view of mechanical pressure, there are no facts at our command regarding the relationship of hydrocephalus of the third ventricle to precocious sexual development. As already outlined, such pressure symptoms develop along the lines of genital atrophy.

One further possibility for a hypophyseal explanation presents itself. It may be that the precocious sexual development may be an early irritative sign of a purely nervous character acting through the pars nervosa sympathetic system, which is very rich, and that later increase in pressure brings about degeneration or atrophic phenomena. Further, Cushing's hypothesis which assumes that dyspituitarism results from lessened pituitary secretions in the cerebrospinal fluid, which results from pressure on the infundibulum, may be the explanation of these sexual changes.

C. CACHEXIA

Whether this has any relation to the pineal, or is a symptom of the hydrocephalus, or of the tumor itself, cannot yet be determined. Attention should be directed to it, however.

REPORTS OF CASES

Having called attention to these features of the pineal syndrome, we would present the history of the following patient, who had a teratoma of the pineal body; we then present abstracts of all the available cases: Marburg collected forty-four in 1909, Pappenheim thirty-seven in the same year. We present histories of fifty-nine cases, some of which are found in the literature of the early part of the last century, which have been overlooked. As we have seen no complete summary of these cases ever presented in any language (Chirone has collected a few) we have felt justified in making such as an addendum to our own paper.

AUTHORS' CASE

History.—R. S., a boy aged 12, of German-American parentage, entered Dr. Pearce Bailey's service at the New York Neurological Institute Sept. 2, 1910, because of failing memory and difficulty in walking. The clinical picture was at first suggestive of juvenile paresis (Fig. 2).

The family history was entirely negative, save that his paternal grandfather had died of paresis in Middletown State Hospital.

His personal history was practically negative. At the age of 5 he broke his right leg in two places, since which time he has always had a stiff leg.

In the early part of 1909, his parents noted that he was not so bright or as quick as formerly; that his school work was not so good as it had been, for he had been a very bright boy. He had grown very rapidly and was markedly fat. His writing for August, 1909, and May, 1910, shows that he had developed during this time a distinct tremor of the hand. In June, 1910, he had a severe attack of vomiting, and his mother ascribed the onset to this "bilious attack." About July, 1910, his mother noted that his right leg was stiffer than usual, and he could not walk so well. In August his legs seemed to give out, and he staggered as he walked and would frequently fall, pitching to one or the other side. His voice had also began to be high-pitched, and a little more feeble, and talking seemed difficult. He was more sleepy than usual, much more quiet, reserved and apathetic, though responsive. His gait became much worse and he occasionally had incontinence of urine. No further character changes were noted by the family, save depression and a tendency to cry. He did not complain much of headache, although he had had some; he felt that the head was heavy; it was hard for him to concentrate his attention. He had had no diplopia nor convulsions.

Examination.—On admission examination showed a boy large for his age, very fat, pale and almost waxy. He had no genital hair, but the chin was slightly downy.

Neurological Status: *Smell* was normal. *Sight* was poor; 20/100 right, 20/200 left. There was marked contraction of the visual fields for white and red in each eye with some interlacing of the color-fields. The fundus examination showed a papilledema of 2 diopters in each eye. The disks were gray and not greatly blurred at the margins.

Third, Fourth and Sixth Nerves: The eye movements upward were completely lost, and the eyes could not be elevated above the horizontal, owing to a paralysis of the associated eye movements for both superior recti. The superior oblique were also affected. Mobility outward was moderately diminished in both eyes. Other movements were normal. There was occasional nystagmus which was irregular, sometimes lateral and at others rotary. The pupils were equal, 4 mm., irregular in outline and reacted sluggishly to light and during accommodation.

Fifth Nerve: Normal, motor and sensory.

Seventh Nerve: Face symmetrical; movements normal, right equal to left.

Eighth Nerve: Hearing was poor. Watch at 4 inches, right equal to left. Rinné and Weber tests normal, right equal to left. The left labyrinth was slightly more irritable than the right to the turning test.

Ninth, Tenth, Eleventh and Twelfth Nerves: Fauces, normal. Tongue protruded slightly to the right, and had a fine tremor. Speech was stumbling. Taste was normal, right equal to left.

Fig. 2.—Author's patient, R. S., from photograph. Head thrown back to show eye position.

Upper Extremity: No atrophy, hypertrophy, hypotonus or spasm; muscular power good; nerve-trunks not tender; triceps and radial reflexes were lively; right greater than left. There was present a coarse static tremor of both hands, together with a good deal of ataxia; no loss of stereognostic sense; sensations uninvolved.

Trunk showed no bony or muscular anomalies. The abdominal, epigastric and cremasteric reflexes were present and equal. No asynergia. No sensory disturbances.

Lower extremities: No atrophy or hypertrophy, but there was slight hypotonus on both sides. Muscular power was fair. The knee- and ankle-reflexes were exaggerated and equal. Ankle-clonus was present on both sides as likewise were the Babinski and Oppenheim reflexes. The gait was spastic, ataxic, and stumbling, swaying more to the right than to the left: Romberg positive; marked ataxia of the legs; slight asynergia, especially walking backward; sensations normal.

The thoracic and abdominal organs were negative.

The urine was entirely normal. The blood gave a negative Wassermann reaction. The spinal fluid showed no excess of globulin, contained no lymphocytes and gave a negative Wassermann reaction.

Mental examination revealed merely a lack of retention in Ziehen's combination memory test, with marked slowing of all responses.

Fig. 3.—Section of brain from patient R. S., showing pineal tumor, hydrocephalus and flattened thalami, mid-brain and optic tracts, also dilatation of infundibulum.

X-ray plates of the head showed a number of shadows in the region of the pineal body, but this was not, at the time, interpreted as being due to the tumor.

A diagnosis of brain tumor was made, but the localization was not definitely decided. We considered it to lie on the left side of the brain, either deep in the substance of the cerebellum or else just above the tentorium, involving the superior cerebellar peduncle.

September 14, the left side of the face was distinctly weaker than the right, and the tongue protruded to the left. The optic disks showed the same degree of edema as before, but their color was fainter, with beginning atrophy.

Following this the patient's gait became very ataxic, so that he had to be helped in walking. Hypotonus was marked, especially in the legs. Incontinence

of urine and feces was almost constant. In the early part of October, it was noticed that when the patient attempted to look up the right eye was elevated a little more than the left (Magendie-Hertwig symptom).

Operation.—A decompression operation was decided on, and the first stage was started by Dr. Elsberg October 5. Profuse hemorrhage from a cut emissary vein caused the operation to be discontinued before the skull was opened.

October 15: Left facial palsy more prominent. Tongue protruded to the left. Arms much weaker than formerly, right much more so than left. Sensations normal. Patient too weak and ataxic to stand.

October 24: Second stage of the decompression operation performed. A piece of bone 3 by 2 inches removed, exposing the left posterior fossa. Dura very tense.

November 1: Definite left hemiparesis, with exaggeration of all reflexes; left greater than right. Patellar clonus on left ankle, left greater than right. Babinski right greater than left. Light and accommodation reactions; right sluggish, left absent. The eye movements had become very peculiar. At rest there was a slight external strabismus. Accommodation for near objects was difficult and in

Fig. 4.—Section of brain from patient R. S., showing hydrocephalus of ventricles, tumor of pineal, and effect of pressure on the corpora and mid-brain.

attempting to produce it the eyes would move around independently of each other. All associated movements of the eyes were seriously affected. At times the right eye would rotate around an anteroposterior axis, the upper pole turning to the right. This was noticed best just as the patient opened his eyes. The left side of the tongue was slightly atrophied. The patient was extremely ataxic, being unable to get out of bed, or to feed himself.

His condition became gradually worse. The eye movements became more and more incoordinated. He did not speak voluntarily, and answered questions with difficulty and in monosyllables. The left hemiparesis continued to increase.

November 28: The third stage of the decompression operation was done and the dura opened. A large amount of cerebrospinal fluid escaped. Nothing abnormal was seen, but the patient's condition did not permit examination of the third ventricle area.

Following the operation the patient's entire left side became very stiff, spastic and rigid, so that it could not be moved. The hand was held tightly clenched,

with the thumb adducted, so that it protruded between the third and fourth fingers. The leg was in much the same condition, but when irritation (pinpricks) was applied to the leg, it flexed sharply, and could not be voluntarily extended. The foot was held in a position of marked talipes equinus. No sensory disturbances were appreciable. An examination of his mental state was impossible on account of his dulness.

The boy became progressively weaker, and died Dec. 12, 1910.

Necropsy.—Post-mortem examination performed by Dr. Casamajor, three hours after death, showed a large amount of cloudy cerebrospinal fluid. The field of operation was clean. The brain presented nothing abnormal except a marked distention of the third ventricle.

Section of the brain, after hardening in formaldehyd solution, showed a large rounded, encapsulated tumor about 1½ inches in diameter, replacing the pineal gland. The tumor was soft and consisted of sebaceous matter, hair and pieces of cartilage (teratoma). These cartilage bits are undoubtedly the structures which caused the shadows on the *x*-ray plates. All the ventricles of the brain were enormously dilated. The corpora quadrigemina were flattened in the dorsoventral direction and the aqueduct of Sylvius was almost obliterated.

Microscopical study of the degenerated fiber tracts has not yet been completed.

SUMMARY OF CASES IN THE LITERATURE

1. Blane's Case.[7]—Officer in navy, who at the age of 33 had slight pain or confusion in the head. More thirsty than usual. Increased. Then came vomiting and pains in balls of eyes when he turned them to either side. He was well for a time when headaches reappeared, mostly in the occiput, sometimes diffused over the whole head. He later had some numbness and weakness of the left hand. After five years he became actively delirious, then lay in a quiet delirium or stupor for fourteen days.

Autopsy showed some hydrocephalus; the nates and testes did not appear distinct, and the situation of the pineal gland was occupied by a hard fibrous tumor, shape and size of a nutmeg, and cut smooth. It lay a little to the right, bruising and mashing the substance of the cerebellum. The pulpy matter adhered to the tumor.

2. Schmidt's Case.[8]—This is the earliest case of value in our present discussion. It has been missed in all of the papers on the pineal gland. It is particularly interesting in that Schmidt refers the cerebral signs to the hydrocephalus, and the retropulsion signs to the quadrigemina. Further, it may be noted that disturbance of the generative system and possibly adiposis were recorded by this observer.

N. A., female, 22 years old, was received in hospital, Aug. 20, 1831. She had had somewhat intermittent headache and dizziness for about a year preceding. At the time of admission the pain had returned with great severity. Coincidently with the beginning of the headache the menses had become scanty and had ceased entirely at the time of admission.

Status on August 22: Patient was anxious and restless; consciousness clear; again she was very quiet, but collected. She had a drunken gait.

August 25: Patient was again dizzy, forced positions of the head, being unable to hold it up at times; convulsive movements in head and extremities, without loss of consciousness. Patient was extremely well nourished, *eine kräftige, fast üppige Ernährung zeigende Kranke*, confined to bed with turgid facies, and the appearance of a dement, or deeply intoxicated patient, with dilated pupils, that

7. Blane, G.: History of Some Cases of Disease in the Brain; Case of a Tumor Found in the Situation of the Pineal Gland, Tr. Soc. Imp. Med. and Surg. Knowl., 1800, ii, 198.

8. Schmidt, P.: Beiträge zur Diagnostik der Krankheiten des Gehirns, Med. Ztg., 1837, vi, 32. Case 2. Enormitas glandulæ pinealis, p. 33.

reacted very slowly to light. Patient could hardly answer questions; but according to the nurse knew her surroundings, and at times talked and ate with appetite; incontinence of urine. Patient made constant retropulsion movements. Lying in bed, she bent her head back; on being forced to stand, she required three persons to prevent her from falling backward, the head being thrown backward continuously.

September 10, she died, after a seizure, during which she ground her teeth violently.

Autopsy showed marked hydrocephalus (4 ounces water in ventricles). A pear-shaped tumor, about 2½ by 1¾ by ½ inches, rose-red in color and about the consistency of the brain white matter, was found occupying the position of the pineal. The tumor had occupied the third ventricle in part. Thalami, corpora striata, chorioid plexus and cerebellum were normal. The corpora quadrigemina on the contrary were much flattened, and practically obliterated. No note on the hypophysis. Schmidt refers to some interesting older cases which do not give enough details for our purposes.

3. Stanley's Case.[9]—M. B., female, aged 4, had been restless and nervous for three weeks, and she had begun to mope a week previously. Four days before

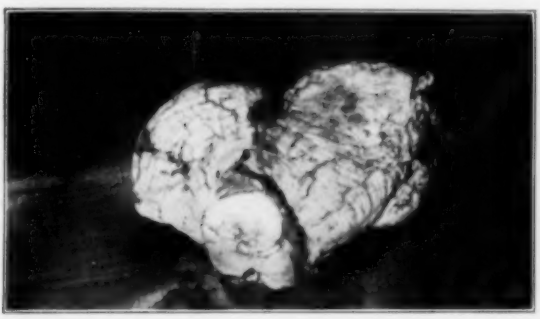

Fig. 5.—Tumor from patient R. S., at cerebellar junction. The tumor sits in a narrow cup at the front of the figure.

64 West Fifty-Sixth Street.

Stanley saw the child she had fallen insensible, remaining so until she died four days later. She had vomited frequently while unconscious. Pulse was 60; the left pupil was fixed and contracted, the right irregularly dilated. No other data. On necropsy a distended pineal gland the size of a hazel-nut was found. It had pressed against the nates of the corpora quadrigemina and laterally against the optic thalamus. The former, as well as the pons, were softened from the pressure.

4. Simon's Case.[10]—Female, 35 years old, had headaches, loss of sight in right eye three years, intense headaches. Not under observation several months; no further clinical notes, and no definite history of the lesion of the pineal beyond title.

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9. Stanley, S.: Dropsy of the Pineal Gland, Lancet, London, 1837, p. 935.

10. Simon, E.: Hémorrhagie de la glande pinéale, Bull. Soc. anat., Paris, 1859, xxxiv, 306.

11. Friedreich: Psammoma Kystomatosum hæmorrhagicum der Glandulæ pinealis in Combination mit Medullarsarkom, Arch. f. path. Anat. (Virchow), 1865, xxxiii.

5. Friedreich's Case.[11]—F. K., 59 years old, hanged himself. He had been depressed for some time, had been drinking heavily, and had had severe headache for over a year and sleeplessness. Cherry-sized tumor of pineal was found.

6. Blanquinque's Case.[12]—D. M., male, aged 39, September, 1868, was taken sick with headache, which became frequent and finally almost continuous by January of the following year. He then noted diminution in his vision. In July he had epileptiform convulsions. His attacks continued, and he became weaker and weaker, showing a marked memory defect. January, 1870, he was confined to bed; his legs would not carry him; he had no paralysis, however. Blindness was complete, pupils widely dilated; papillary atrophy; conjugate deviation below and to the right but no oculomotor palsies. He died in a convulsive attack.

Necropsy showed marked hydrocephalus; veins of Galen engorged with blood; tumor size of pigeon's egg; psammoma pressing on posterior corpora quadrigemina of the right side.

7. Massot's Case.[13]—G. B., aged 19, a man with polyuria and polydipsia of gradual onset; he drank 25 to 28 liters of liquid a day. Three months after entering the hospital he had an epileptiform convulsion; two months later he had violent headaches, which continued, mostly frontal and temporal; then left internal strabismus, with loss of ability to look up, diplopia and slight diminution in vision. The mental processes became retarded. Patient grew progressively weaker, and his legs could not support him. Sensibility was intact. Vomiting then set in. His memory gradually failed, and six months after his entrance he died in coma.

Autopsy showed hydrocephalus, particularly of the left ventricle, a hard mass in front of the corpora quadrigemina, occupying the position of the pineal. The tumor entered the third ventricle. It was 3.3 by 3.0 by 2.8 cm., and was a carcinoma of the pineal.

8. Bouchut's Case.[14]—G., 2 years of age, female, entered hospital in poor physical condition. Her head was large, the fontanelles markedly dilated, and pressure caused pain. There was conjugate deviation of the eyes; the pupils were slightly dilated, and sluggish to light. There was commencing atrophy of both disks. The upper extremities were contracted. The child did not talk and was semistuporous. She had had some indefinite convulsive seizures before admission to the hospital. Two weeks after entry she died in coma, with convulsions, during which she had nystagmus.

Necropsy showed marked hydrocephalus. There was a cystic pouch in the posterior portion of the third ventricle. The iter was flattened or obstructed by the walls of the cyst, and it had pressed on the corpora quadrigemina. It was a cyst of the pineal gland.

9. Schearer's Case.[15]—S. S., a 16-year-old girl, had epilepsy from childhood; no neurological history. Necropsy showed sclerosis and a small tumor of the pineal the size of an almond.

10. Weigert's Case.[16]—Teratoma of the pineal gland. Boy 14 years old. No history. The tumor had grown mostly forward into the third ventricle. There was some hydrocephalus.

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12. Blanquinque, P.: Tumeur de la glande pinéale, Gaz. hebd., 1871, p. 532.

13. Massot, M.: Note sur un cas de tumeur cérébrale avec polyurie, Lyon méd., 1872, x, 373.

14. Bouchut, M.: Obs. II. Kyste séreux du troisième ventricle, Gaz. d'hôp. 1872, xliii, 353.

15. Schearer: Enlargement of the Pineal Gland and Sclerosis of Brain in a Case of Chronic Epilepsy with Amentia and Aphasia, Edinburgh Med. Jour., 1875, xxi, 297.

16. Weigert, C.: Zur Lehre von den Tumoren d. Hirnanhänge, Virchow's Arch. f. path. Anat., 1875, lxv, 212.

11. Duffin's Case.[17]—W. C., a groom, aged 25; negative history; two months prior to admission had dragging at back of neck and occasionally pain in occiput to forehead; deep-seated aching in orbits; attacks of vertigo and unsteadiness in gait. Objects swam about, but without definite direction. Headache gradually increased, and there was gradual impairment of sight. A month later, he saw double. At time of admission headache was intense; giddiness was excessive; he could not stand, and when supported staggered like a drunken man; closure of eyes aided his gait; head was retracted; lower limbs normal; subjective noises in ears; good intelligence; pupils were large, equal, and reacted sluggishly to light; slight right internal squint; swollen disks, right greater than left; slight facial palsy. Three weeks after admission, drowsiness was marked and a nocturnal delirium set in; later there was continuous mild delirium, with coma and death.

Necropsy showed hydrocephalus, with clear greenish serum in the ventricles. Tumor 2 by 1½ inches, chiefly in third ventricle, pressing on the thalami, and also on corpora quadrigemina, encroached on right superior cerebellar peduncle; some absorption of the optic thalamus; tumor had penetrated into aqueduct of Sylvius. It was a glioma of the pineal, apparently.

12. Nieden's Case.[18]—E., a 35-year-old woman, complained of seeing badly, and double vision, at times with marked giddiness; occipital headache of late. She spoke slowly and gave the impression of weak-mindedness. There was paresis of the right trochlearis, with diplopia, especially on looking down, and to the right; papillæ normal. Two months later, seen in another hospital, the patient was in a delirious state, and she shortly died.

Necropsy showed large walnut-shaped cystic pineal gland, filling up the entire third ventricle.

13. Falkson's Case.[19]—O. B., aged 16, complained of difficulty in seeing and double vision, the latter developing shortly before coming to the clinic. He was a strongly built boy of middle size in a good state of nutrition; face full-blooded, especially the nose; eyes showed slight paresis of the superior recti of both eyes, and left rectus internus paresis. Hearing was markedly affected; he was forgetful, slow in his movements; no other motor or sensory disturbances. He was very drowsy and would go to sleep while being treated. Shortly before his death papillary changes were noted.

There was flattening of the convolutions and marked hydrocephalus interna and externa. The chief part of the tumor was in the third ventricle, 5.8 by 3 by 4.7 cm. Cyst of pineal; thalami excavated; compression of corpora quadrigemina.

14. Nothnagel's First Case.[20]—A 21-year-old man had had epileptic attacks from childhood, occurring two or three times a year only. Attacks ceased one year before beginning of latter difficulty, which came on with vomiting which became continuous. The patient did not complain of headache, but was forgetful and mentally dull, and had vertigo. He gradually lost strength and commenced to walk with staggering gait, and could hardly stand. A few months later his eyes became immobile, and the pupils were dilated. Two years after the beginning of the symptoms he was taken into the clinic. The patient was a medium strong man, blind, with fixed gaze, somewhat thin, semicomatose, but was aroused when spoken to; could tell his name, etc. No palsies were apparent, but the patient was unable to stand up or sit up. He died in coma.

Necropsy showed hydrocephalus, sarcoma of the pineal, involving the quadrigemina, pushing into the third ventricle, involving the posterior end of the optic

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17. Duffin, A. C.: Tr. Lond. Clin. Soc., 1876, ix, 183.

18. Nieden: Fall von Tumor (hydrops cysticus) glandulæ pinealis, Centralbl. f. Nervenh. u. Psychiat., 1879, ii, 169.

19. Falkson: Ein Chondrocystosarcom im dritten Ventrikel, Virchows Arch. f. path. Anat., 1879, lxxv, 550.

20. Nothnagel: Topische Diagnostik der Gehirnkrankheiten, 1879, p. 206.

thalamus, posteriorly reaching the cerebellum. The aqueduct was apparently dilated.

15. Gowers' Case.[21]—R. P., aged 24, after exposure to the sun as a policeman, developed a headache which became severe. He had it less severe for a month; there was slight mental dulness and paralysis of one sixth nerve; patient dozed most of the time, attention being aroused with difficulty; partial paralysis of right external rectus only. The pupils were equal. Two weeks later the patient did not answer questions and gradually became deaf. Double optic neuritis occurred; a week later incontinence of urine developed; pulse became infrequent, 50 to 60. There was a rise of temperature to 100. The patient stayed in semicoma, the right side of the face gradually becoming paralyzed. He died after nine weeks from exhaustion.

Necropsy showed a sarcoma between the optic thalami posteriorly, in front of the corpora quadrigemina, which were damaged, 1½ by ¾ of an inch in size. The pineal body was gone; the left corpora quadrigemina were destroyed, tumor extended into iter.

16. Wernicke's Case.[22]—Wernicke speaks of a patient affected similarly to Blanquinque's.

17. Turner's Case.[23]—Museum specimen. No case history.

18. Feilchenfeld's Case.[24]—L., aged 18, Feb. 2, 1885, was admitted to hospital; ten months previously had headache, vertigo and vomited; became apathetic and showed great weakness of the lower extremities; had jerky movements of the entire body, becoming so bad as to interfere with his eating and drinking; frequent diplopia and involuntary urination and defecation. Patient had complete paralysis of the ocular muscles, the eyelid alone being movable. Pupillary reactions showed the right pupil wider than the left; double choked disk; slight left facial palsy. Upper extremities showed slight ataxia, also in lower with diminution of motor power; sensibility intact; skin and patellar reflexes present; clonus right side. Patient had gradually rising temperature and died in a comatose condition.

Necropsy showed marked hydrocephalus; aqueduct not dilated. A softened part about the size of a 20-mark piece (or a 5-dollar gold piece) at origin of middle and superior cerebellar peduncles, incorporated with swollen, sarcomatous pineal tumor; also involving the anterior end of the corpora quadrigemina.

19. Pontoppidan's Case.[25]—A. S., aged 31, received in the clinic last of May; had had headache and vertigo for two months; for fourteen days suddenly worse, with mental dulness, unable to walk or stand and had involuntary excretions. On admission patient was mentally dull, with tremor of extremities; some loss of motor power in the left; pupils dilated, reacting slowly; movements of eye diminished in all directions; papillary margins indistinct; patient showed tendency to lie on one side; could walk if supported, with tendency to retropulsion (gait cerebellar). During stay in hospital, there was increasing dulness, increased sweating, opisthotonos, epileptiform cramp, optic neuritis, conjugate deviation of eyes to right.

Necropsy: Marked hydrocephalus. Walnut-sized sarcoma of pineal lying on corpora quadrigemina, compressing them.

20. Schulz's Case.[26]—N. N., male, aged 28, began to have severe headaches in 1883. In March, 1884, he was seen by a physician. He had been compelled to

21. Gowers: Cases of Cerebral Tumor, Lancet, London, 1879, i, 363, Case 3.

22. Wernicke: Lehrbuch der Gehirnkrankheiten, iii, p. 299.

23. Turner, F. C.: Spindle-Cell Sarcoma of the Pineal Body, Containing Glandular and Carcinomatous Structures, Tr. Path. Soc., London, 1885, xxxvi, 27.

24. Feilchenfeld, L.: Ein Fall von Tumor cerebri, Neurol. Centralbl., 1885, iv, 409.

25. Pontoppidan, K.: Ein Fall von Tumor der Zirbeldrüse, Neurol. Centralbl., 1885, iv, 553.

26. Schulz: Tumor der Zirbeldrüse, Neurol. Centralbl., 1886, v, 439.

stay in bed since January for bad headaches, especially in the occipital region. Holding the head forward seemed to relieve them. There was a sensation of bursting in the head; failing sight, especially left; papillæ at that time not swollen, but margins not sharp. Status at that time: Strongly built man with somewhat staring eyes, percussion on occiput painful; pupils normal, no motor or sensory symptoms. Patient was better until April, when he began to stagger in his walk, and could not go alone. In September he began to grow worse; the exophthalmos was more marked, and the right eye had a tendency to turn outward.

In 1885 the tendon reflexes of the upper extremities began to increase somewhat. Swallowing was precipitate. The patient had to hold his head forward. December, 1885, patient was in bed; no fever, head forward, chin on chest, face red, somewhat cyanotic, eyes injected, exophthalmos, pupils equal, reacting, no ocular palsies, no facial palsies, no palsies of leg or arm, light paresthesias of feet and right arm; unable to walk; marked increase of knee-jerks and clonus on both sides; headache was intense. Patient died.

Necropsy: Marked hydrocephalus; glioma of the pineal, walnut-sized, fairly hard, which lay on the corpora quadrigemina, compressing and somewhat shoving them apart.

21. Reinhold's Case.[27]—O. D., male, aged 19, always sickly, much headache and vertigo, easily tired; seven months previously there was swelling of the testicles, which changed from one side to another, occasional painful urination and polyuria. Jan. 4, 1884, the patient was awakened by severe giddiness and headache, and on the days following was chilly and weak; headache remitting, appetite poor; five days later there was vomiting, and on the twelfth the patient entered the hospital where the vomiting continued, and headache increased. The disks were normal at this time. On January 19, he had a mild convergent strabismus, due to weakness of the left rectus externus; pulse slowed to 60; increase of skin and tendon reflexes of lower extremities; patient said that he did not see so well as formerly; then a slight right facial palsy gradually developed, and lack of coordination of the ocular and lid movements looking downward; slight exophthalmos, pulse slow. On January 31, patient had a convulsive seizure, mostly of right side of body. The movements of the eye muscles became less and less, and nystagmus-like movements began; pupils were equal; facial involvement increased, and there was slight impairment of hearing. February 6 double ptosis occurred; paresis right abducens was more marked, the left eye not being movable beyond the middle line. Sleepiness and mental dulness became more and more marked; patient smeared himself with feces. February 15 he was unconscious, pupils immobile, pulse 42, involuntary urination; two days later, another attack, with respiration of 10; two days later, pupils unequal, left larger than right, patient semicomatose. Patient died February 20.

Necropsy: Hydrocephalus, flattening of the mid-brain and pontine region, hazel-nut-sized cystic tumor of the pineal, just above posterior commissure. The corpora quadrigemina were pushed backward, flattened, and pushed apart, the aqueduct being shut off. The left middle cerebral peduncle was also compressed, and both abducens nerves flattened.

22. Coats' Case.[28]—J. M., boy aged 13; meager history; came in on September 30, and died October 13; was very drowsy; could be awakened and would look around languidly and then go to sleep again; had been drowsy about five months; no fits; some weakness of the right internal rectus, and slight droop of left eyelid; mouth slightly drawn to the left; could walk stiffly and incoordinately only by being supported; urinary incontinence; epileptiform fit just before death.

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27. Reinhold: Ein Fall von Tumor der Zirbeldrüse, Deutsch. Arch. f. klin. Med., 1886, xxxix, 1.

28. Coats, J.: An Adenoid Sarcoma with Cartilage Originating in the Pineal Gland, Tr. Path. Soc., London, 1887, xxxviii, 44.

Autopsy: Hydrocephalus, tumor 1⅞ by 1⅝ by 1¼ inch, pushed into third ventricle, aqueduct and fourth ventricle; flattening of thalami; small pieces of cartilage.

23. Daly's Case.[29]—W. O., male, aged 23, developed headache and photophobia after a supposed lightning stroke in October, 1885. He was seen three weeks after this occurrence. He then walked with a staggering gait (drunken), being worse on closure of the eyes. The arms were free, and the tendon reflexes were normal. Vision was dimmed, pupils dilated, equal, contracting sluggishly to light and accommodation. Double optic neuritis with swollen disks existed. The patient vomited constantly. Ten days later he developed palsy of the left external rectus, and nine days after that, right facial palsy. During this month and the next he had spasmodic contractions of the muscles of the limbs and trunk from time to time. He was confused and pugnacious. In February, 1886, the hearing in both ears was defective; the patient was almost blind and had occasional fits. He could stand and walk only with assistance, but there were no palsies. His appetite was enormous, and he gained greatly in weight (5 stone or 70 pounds). His intelligence diminished; he became entirely deaf, and lost control of bladder and rectum. He died in coma in May, 1886.

Necropsy showed an alveolar carcinoma of the pineal 2 by ¾ by ½ inches, lying on the corpora quadrigemina, which were soft and flattened. No mention is made of hydrocephalus.

24. Nothnagel's Second Case.[30]—S. R., male, aged 17, in 1883 fell from a ladder, was unconscious a few hours, vomited and had headaches; was sick for several weeks with fever, headache, vertigo and constipation. On recovery he still had headaches. Three months later he had attacks of vertigo; he swayed and fell, usually backward. His gait disturbance became very marked, he walked with wide-spread feet, and uncertainty. He had some increased urination and thirst. Patient also noted that his head was growing larger. The pupils were dilated; left more than right; reaction slow; ocular, facial and tongue muscles intact; hearing good, papillæ pale, edges indefinite, Romberg marked. Fifteen months later he again entered the clinic. At this time the pupils were equal, dilated, reaction to light and accommodation slow; patient blind in right eye, little sight in left; gait uncertain; patellar reflexes increased on both sides; no clonus; no sensory disturbances. Later he had vertiginous attacks. Three months later he was again studied with the history that vertigo and headache still continued, and convulsive seizures developed. These were epileptiform in character. During this time the patient had developed into a large, strongly built, strikingly fat young man; musculature was weak; memory and intelligence not impaired.

In 1885 he was totally blind. In 1886, the papillæ were atrophic, pupils wide, reacting slowly, later very wide and non-responsive to light or accommodation. Nystagmus on looking to right; later on looking upward. Smell later diminished; other cranial nerves normal. The gait retained its stumbling, staggering (drunken) character. The knee-jerks were increased, clonus developed in August, 1885, and then spasticity became marked. No sensory anomalies. Ringing in the ears had occurred early. In August, 1887, he commenced to discharge cerebrospinal fluid from the right nostril, after a period during which he vomited frequently. The amount varied from 12 to 110 c.c. a day for seventeen days. When checked the symptoms of pressure increased (compare Meyer case) to coma, involuntary urination, defecation, slowing of the pulse, etc. The patient died in October, 1887, four years from the date of the initial symptoms, after the fluid had ceased to flow for thirteen days.

Necropsy showed marked hydrocephalus; the aqueduct was choked, and in the place of the corpora quadrigemina there was a hard, hazel-nut-sized tumor 0.5

29. Daly: A Case of Tumor of the Pineal Gland, Brain, 1887-1888, x, 233, Case II.

30. Nothnagel, H.: Geschwülst d. Vierhügel; Hydrocephalus, Abfliessen v. Cerebralflüssigkeit durch die Nase, Wien. med. Bl., 1888, xi, 162.

by 1.3 cm., which had compressed the aqueduct. It had sunk into the quadrigemina, spreading them apart. It was a glioma, apparently, of the corpora quadrigemina.

25. GAUDERER'S CASE.[31]—A 12-year-old boy, exceedingly well nourished, somewhat pale, had been noted the previous summer to be restless; he slept badly and had an aural discharge. Four days before admission he complained of headache, fatigue, and occasional vomiting, but continued going to school, until an increase in the symptoms brought him to the clinic.

Here he lay in bed, was somewhat apathetic, with a fixed expression, and answered questions slowly, but clearly. He complained of frontal headache and pain in the neck in forward movements of the head. Pressure on the neck was painful. The pupils were medium wide, reacted sluggishly to light; no facial palsies; patient's movements were slow and careful; abdominal reflexes active, no complete sensory examination; patellar reflexes absent, but plantar and cremasteric reflexes present.

The patient continued in this condition with slowed, small, and, at times, irregular pulse. He lay sleeping most of the time but could be aroused, and gave pertinent answers. There was slight opisthotonos. There was beginning neuritis in the right eye two weeks after entrance to the clinic. The patient's stupor gradually increased from day to day, slight fever developed and patient died in coma fourteen days after coming into the clinic.

Necropsy showed marked hydrocephalus, including the infundibulum; the corpus callosum was pressed on; the corpora quadrigemina were partly destroyed by a cystic teratoma of the pineal (walnut-sized), 3.5 by 2.5 cm., which projected partly into the third ventricle, and also compressed the thalami.

26. KNY'S CASE.[32]—J. H. W., male, aged 32, in April, 1881, had a sudden sticking pain in occipital region which gradually spread over the skull during the course of the year; since July, 1882, ringing in the ears and painful thumping on the inside of the skull. The pain would exacerbate at times, and be accompanied by vertigo, blackness before the eyes, general tremor and clouding of consciousness for hours. In the fall of 1882 the patient's vision become dimmed, so that by November he could not read, and a month later could not get about. Double choked disk was then present. The patient was transferred to the medical clinic where attacks became stronger, resembling epileptic convulsions, with immobile pupils, but the condition remained about the same, up to 1884 when nystagmus developed and slowed speech. In 1885 his intelligence suffered. In 1886 he was still well nourished, abdomen very fat, lay apathetically on the back; marked divergent strabismus, dilated pupils, immobile to light, and marked lateral nystagmus were present. The patient could not stand; fell backward; no palsies; sensibility normal; patellar reflexes normal. In the last months there was increasing stupor, involuntary urination and defecation; patient remained fat to the end; pupils widely dilated; bulbi extending, divergent; epileptiform attacks; sudden rise in temperature and death.

Necropsy: Marked hydrocephalus, walnut-sized sarcoma of pineal; the corpora quadrigemina only slightly compressed. Vena Galeni widely dilated.

27. ZENNER'S CASE.[33]—G. W., boy aged 13, began to have intermittent headaches in July, 1891, usually coming on each morning, letting up during the day. They were mostly temporal, less often occipital or frontal. Not infrequently there was vomiting. He then commenced to stagger while walking (drunken gait); his head was drawn back to the left side; vision soon became impaired, and by November he was blind. His hearing grew progressively bad; speech began to

31. Gauderer, L.: Zur Casuistik der Zirbeldrüsentumoren, Inaugural Dissertation, Giessen, 1889.

32. Kny: Fall von isolirtem Tumor der Zirbeldrüse, Neurol. Centralbl., 1889, viii, 281.

33. Zenner: A Case of Tumor of the Pineal Gland, Alienist and Neurol., 1892, xiii, 470.

be indistinct and finally became unintelligible. In October he began having peculiar tonic paroxysms, with periods of unconsciousness, which lasted from one to thirty minutes. He was confined to his bed by November, becoming more and more stuporous, soiling his bed. Then there developed slight contraction of the left arm.

In March, 1892, patient was emaciated with rapid pulse, in a semi-stuporous state; no paralysis, but marked contracture of arms; pin-prick felt; pupils dilated, immobile to light; eye movements apparently free; double optic neuritis. The patient did not speak at all. He died in tetanic spasms in April, 1892.

Autopsy showed a marked hydrocephalus, and a large gliosarcoma of the pineal gland, 1¾ by 1¼ inches in size, lying mostly in the ventricles.

28. SCHMID'S CASE.[34]—J. K., male, aged 21; tuberculous patient with fever; no mental or neurologic signs for four months preceding death; under hospital observation.

Necropsy showed gelatinous tumor of pineal resting on corpora quadrigemina. Size not given.

29. KÖNIG'S CASE.[35]—Accidentally found tumor at autopsy in a man aged 45; psammo-sarcoma, gelatinous, large as a chestnut, with dilatation of third and fourth ventricles and posterior cornua.

30. GUTZEIT'S CASE.[36]—A boy aged 7¾ years, who for about eight months before his death was taken with frontal headache and vomiting; isolated attacks of vomiting had occurred previously. A month later (January, 1893), he had double vision, staggering gait, and drowsiness. In March he had disturbance of hearing, saw spots before his eyes. The patient was "strongly built and in a good state of nourishment." He wanted to eat all of the time, was somewhat stuporous, and yawned a great deal. His movements were uncertain, ataxic; pulse was retarded; optic neuritis, and paresis of the left rectus internus were present; patient could not look downward; had strong horizontal nystagmoid movements on looking up. Pupils were small, unequal, left smaller than right; immobile to light and to accommodation. Hearing was diminished. Incontinence of feces and urine was present; now and then spasms in facial muscles; pubic folds well developed.

Necropsy: Teratoma of the pineal, 4 by 3.25 cm., with marked hydrocephalus of the ventricles. The tumor extended into the third ventricle, pushing the thalami aside. The corpora quadrigemina were markedly flattened.

31. HOESSLIN'S CASE.[37]—E. K., boy, aged 9, had had marked thirst and polyuria for some time. He drank from 20 to 24 quarts of water a day. At first consultation he had no cerebral symptoms. Some time later, in April, he began to have severe headaches, and frequent vomiting; he staggered and swayed so that he could not walk. Visual defects then developed; no paralyses, but strength of lower extremities was much reduced; the gait was stumbling; the pupils widely and equally dilated; the eyes could be directed to the left, right and down; but the motion up did not go beyond the horizontal. There were also isolated palsies of both superior recti, superior oblique and of the sphincter, and choked disks on both sides. The patient gradually grew weak, and became blind; convulsions set in, and he died following an attack. The diabetes insipidus had diminished some weeks before his death.

Necropsy showed marked hydrocephalus, and a walnut-sized sarcoma of the pineal, which reached over the corpora quadrigemina, and the fore part of the cerebellum, and was attached to the former structures. It was very soft. The corpora quadrigemini were hardly recognizable, being completely flattened and

34. Schmid: Ueber latente Hirnherde, Arch. f. path. Anat. Berl. (Virchow), 1893, cxxxiv, 71 (93), Case xxxii.

35. König: (From Chirone.) Dissert. München., 1894.

36. Gutzeit: Ein Teratom der Zirbeldrüse, Königsberg Dissertation, 1896.

37. Hoesslin, v. R.: Tumor der Epiphysis Cerebri; Diabetes insipidus; Oculomotoriuslähmung, München. med. Wchnschr., 1896, xliii, 292.

softened on the upper surface. The aqueduct of Sylvius was deformed—disfigured. The fourth ventricle was dilated.

32. LORD'S CASE.[38]—Case of syphilitic enlargement, 2.1 by 1.6 by 0.9 cm.; woman insane seven years; epileptiform attacks and fits of violence; eventually left hemiplegia; later, right leg; for a long time demented and in stupor; two accessory gummatous growths.

33. CAMPBELL'S CASE.[39]—1. Patient female, aged 33, epileptic; died of tuberculosis; no brain lesion; pineal 1.0 by 1.3 by .08 cm., a cyst. No history.

34. CAMPBELL'S CASE.—2. Patient, female, epileptic; no history.

35. RUSSEL'S CASE.[40]—1. Female, aged 23, with fracture of base of skull. Post-mortem examination showed cyst of pineal ⅜ inch in diameter. No history.

36. RUSSEL'S CASE.—2. Another museum case. No history.

37. GARROD'S CASE.[41]—Boy, aged 16, died of diabetes. Cyst size of pea. No symptoms; brain normal.

38. LAWRENCE'S CASE.[42]—Patient, 16-year-old boy had cough and headache two days before death; delirium a week before, with pupils widely dilated, and irresponsive, nystagmus, blurring of right optic disk, limbs in constant athetoid movements, no convulsions.

Necropsy showed tuberculous meningitis and swollen gliomatous pineal, 1.4 by 0.7 cm., pressure on upper side of cerebellum.

39. OGLE'S CASE 1.[43]—Diffuse sarcoma of half cortex.

40. OGLE'S CASE 2.—Dr. Ogle's second case is of interest in this respect, as he was one of the early observers to call attention to the changes in the generative organs. The patient was a boy, F. W., aged 16, who had been sick for a couple of months before admission to the hospital. His manner had become strange; he was given to masturbation, and inclined to sleep a great deal. He was well nourished. His gait was staggering, but the reflexes were normal; there was no tremor and no paralysis anywhere; the back, especially the back of the neck, was held stiffly. Ten days after admission the pupils were only slightly active to light and were large, but variable in size; the boy saw perfectly. There was some loss of power in the external rectus of the right eye. About a week later, both external recti were inactive, the pupils widely dilated and inactive to light, and the boy quite blind. Although no choking of the disk was to be seen, there was slight pallor and blurring as from optic neuritis of slight degree; no other cranial nerve involvement; some priapism. The knee-jerks were at first present, but later disappeared; there were no changes in temperature. The penis was of large size, fully equal to that of a lad of 16 or 17 years; pubic hair was fairly plentiful, but the testicles did not seem enlarged.

Until his death, the patient had frequent attacks of vomiting, and frequent fits, marked especially by opisthotonos; but the most striking symptom was sleepiness. He would sleep night and day almost continuously, but could easily be aroused by a question, and by slight shaking, and then would answer with perfect readiness and intelligence, but would fall asleep again if left alone.

Necropsy showed a globular tumor 1 inch in diameter, projecting into the third ventricle, the thalami were pushed apart and hollowed. The corpora quadrigemina were obviously flattened. The tumor was a teratoma.

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38. Lord: The Pineal Gland, Tr. Path. Soc., London, 1899, l, 18.

39. Campbell: Notes on Two Cases of Dilatation of the Central Canal or Ventricle of the Pineal Gland, Tr. Path. Soc. London, 1899, l, 15.

40. Russel: Cysts of the Pineal Body, Tr. Path. Soc., London, 1899, l, 15.

41. Garrod: Pineal Cyst, Tr. Path. Soc., London, 1899, l, 14.

42. Lawrence: Tumor of the Pineal, Tr. Path. Soc. London, 1899, l, 14.

43. Ogle, C.: Sarcoma of Pineal, Tr. Path. Soc., London, 1899, l, 4.

41. HEUBNER'S CASE.[44]—Heubner showed a photograph of a 4½-year-old boy, with body development of an 8- to 9-year-old boy—large penis, scrotum and testes, as in puberty; pubic hair strongly developed; laryngospasm early in life; speech slow in development; after 7½ months this became normal. The increase in growth had taken place in one year, and choked disk had developed at the same time. Mild paretic symptoms appeared, owing to rapidly developing hydrocephalus.

The symptoms were thought to be due to a hypophysis tumor; *x*-ray showed a shadow. Necropsy revealed a pineal tumor, the shadow being due (?) to thinning of bone from hydrocephalus (see case of Oestreich and Slawyk).

42. OESTREICH AND SLAWYK'S CASE.[45]—P. M., boy aged 4, had attacks of a convulsive nature at the age of 12 months. At about 3 years the child, previously active, was quiet and shy, and cried a great deal. The child began to grow rapidly, the penis particularly. Four weeks before entering the clinic the gait was uncertain and difficult. There seemed some mental confusion, the child staring forward and answering no questions. This behavior would come on in attacks lasting a day or so.

The patient was large for his age, with large bones, strong muscles and quite fat. He answered questions. Pulse was regular, 70. There was slight right convergent strabismus; slight nystagmus on side movements; pupils equal; reacted slowly and incompletely to light and convergence; typical choked disk on both sides; child apparently saw badly. Hearing was good; other cranial nerves normal. Mammary glands large; colostrum could be expressed; testicles were size of pigeon's egg; penis large, 9 cm. long at rest; pubic hair 1 cm. long and dark; gait spastic; skin and tendon reflexes active; no loss of muscular power; sensibility intact. Gradually the child became more and more dull; answered questions more and more slowly, and finally would only shake the head. Ataxic movements of both extremities then developed, and finally the child could not sit up, nor eat. Two weeks after admission clonic-tonic convulsions occurred, the reflexes became extremely active, dermographia was marked. About six weeks after admission, the child died in coma and convulsions; radiograph showed a distinct shadow, thought to be the hypophysis.

Necropsy showed a large cystic tumor lying in the third ventricle, about the size of a small apple. There was marked hydrocephalus. Anatomically it showed itself to be a psammosarcoma cysticus of the pineal gland.

The author calls attention to the possible relation of the gigantism to the gland. Askanazy diagnosed this as a teratoma.

43. NEUMANN'S CASE.[46]—A. P., aged 27, had had frontal headaches for seven weeks. Mornings he was nearly free from pain, but it mounted up after an hour or two. Five days before coming to the clinic he had begun to note a diminution of his hearing and his sight, especially of the right side. He also began to see double. Otherwise he was well.

Retinal examination showed marked choked disk, both sides, with diminution of vision; fields could not be tested. The patient was unable to raise the eyes above the horizontal line, or to the right. Movements down and to left were undisturbed. The right eye could not be moved beyond the middle line alone, but the left alone was freely movable. There was marked nystagmus both by convergence and divergence. The right pupil was wider than the left. Both dilated and did not react to light or to accommodation. Hearing was diminished on the left side, otherwise normal; gait normal; no tremors, no ataxia.

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44. Heubner: Demonst. Versamml. d. Naturforsch. u. Aerzte., Dusseldorf, Sept. 22, 1898. Allg. med. Central-Ztg., 1899, lxviii, 89.

45. Oestreich and Slawyk: Riesenwuchs und Zirbeldrusengeschwulst, Virchows Arch. f. path. Anat., 1899, clvii, 475 (Heubner's Case).

46. Neumann, P.: Ein neuer Fall von Teratom der Zirbeldrüse, Inaugural Dissertation, Königsberg, 1900.

About two weeks after admission the patient had his first attack of vomiting. The condition gradually grew worse, and the patient grew thin and sleepy, began to be dizzy in walking, and rapidly became comatose. One month after admission he died in coma, with some elevation of temperature.

Necropsy showed a tumor, mostly lying in the third ventricle, 4 by 3 by 2.5 cm. directed anteriorly to the right, and posteriorly to the left, compressing the thalami laterally, and the corpora quadrigemina below, and pushing them backward. The posterior corpora quadrigemina had almost escaped. The fourth ventricle was dilated. There was marked hydrocephalus. The tumor was a teratoma.

44. HEMPEL'S CASE.[47]—M. L., a baker, aged 24, had been previously well save for an accident to head, followed by occasional headache. His father first noted an increasing slowness in his work. The patient said that his memory was not so good as formerly, and his headaches were more frequent. For the previous year he had been weak, and his gait had become irregular, and like that of a drunken man. There was also ataxia in the arms. One day he suddenly fell down. After a few weeks in a hospital he seemed better, but fell the day of his discharge. He then grew worse and worse and was sent to the state asylum. Examination at that time showed a vacant expression, pupils medium, left larger than right, non-responsive to light, but prompt to convergence; no nystagmus and no eye palsies; tremor of tongue; slight speech disturbance; coarse tremor of upper extremities; increased patellar reflexes, double ankle-clonus; ataxic gait; no change with eyes closed; Romberg; sensibility practically normal; slight hyperalgesia. The patient remained apathetic, the tremor increased, until he was unable to write; reading was difficult; spontaneous speech was slow, not scanning, lip movements very active. The patient was stupid; could multiply and divide, but could not add nor subtract; no papillitis; slight pallor.

About two months after admission he had spasms in the left arm and leg; the reflexes were increased. He gradually developed contractures in the extremities and after five months lay in bed all drawn together; almost unable to move hand or foot; turned head and spoke slowly, could swallow liquids; rotatory nystagmus developed. He grew weaker and weaker and died, eight months after admission.

Necropsy showed marked atrophy of the body, and marked hydrocephalus of the lateral ventricles, but not of the third or fourth. In the posterior pole region there was a tumor which pressed on the veins of Galen. It was about the size of a hen's egg, with its thin end pressing into the third ventricle. It had pressed into the substance of the optic thalami. The corpora quadrigemina were totally flattened and destroyed, the geniculate bodies pushed aside, and the cerebral peduncles much flattened. The tumor was a solid epithelial carcinoma.

45. NEUMANN'S CASE[48] 1.—Patient was a woman, aged 28, first seen March, 1899, for menstrual anomalies, pressure on head which radiated to teeth and neck, principally of the left side; she was much prostrated, was very sleepy, and had a ravenous appetite. These symptoms she had had for three months; no other cerebral symptoms. There was slight difference in the pupils, left larger than right, slight exophthalmos; looking upward caused internal convergence; no diplopia; indefinite weakness of the left facial; beginning optic neuritis, right more than left. After three weeks the pupils had become widely dilated and immobile to light; right hand weaker than left; patellar reflexes both weak, left more active. The patient then had some nausea and severe headache. After a short stay at home she returned after five weeks. In May she was much worse. Headache, vomiting, dimness of vision were worse, and the patient was now

47. Hempel, K.: Ein Beitrag zur Pathologie der Glanduli pinealis, Inaugural Dissertation, Leipsic, 1901.

48. Neumann, M.: Zur Kenntnis der Zirbeldrüsengeschwülste, Monatschr. f. Psychiat. u. Neurol., 1901, ix, 337.

hardly able to stand. Immobile pupils; left eye closed; protrusion of left bulb; pulse rapid, 128. Patient died in June, clear in mind.

Necropsy showed marked hydrocephalus. A thin membrane was found in the third ventricle, lying on the corpora quadrigemina, which could be blown up, showing a bladder shape, 3 by 5 cm. The corpora quadrigemina were markedly flattened. The opening of the aqueduct was enlarged, but nevertheless not permeable because of a small, hazel-nut-shaped tumor lying just behind the posterior corpus quadrigeminum. The medulla was flattened. During life there was a large cystic, hydropic pineal gland. The tumor within the canal was a neuroglioma.

46. Neumann's Case 2.—A boy, aged 11, was well up to eight days before coming to the clinic, when he had severe headache, giddiness and vomiting, and had to leave school. In the clinic the case resembled a tuberculous meningitis; fever, slowed pulse, vomiting. There was diplopia, disappearing on convergence; no pareses. The patient soon became somnolent and died two days after coming to the clinic, with increasing temperature.

Necropsy showed enlarged brain, marked hydrocephalus, dilated third ventricle, filled with walnut-sized (4.6 by 3.4 by 3.0 cm.), reddish, cystic sarcoma of the pineal, fastened to the corpora quadrigemina and to the cerebellum and tela choroidea. The thalami were flattened. The aqueduct was pervious. There was slight development of the external genitals.

Neumann has collected and tabulated reports of twenty-two cases with a full discussion of the symptoms to this date.

47. Joukovsky's Case.[49]—This female child was apparently dead at birth, but was reanimated. She did not cry, however. She slept twenty-four hours after the first bath, and showed no desire to nurse. There were no marked cranial anomalies. At the end of six days there was no exophthalmos, but the pupils were unequally dilated, the left double that of the right. The pupillary reflexes were absent. There was slight divergent strabismus; no nystagmus, but ptosis. The temperature was subnormal. The pulse became slower—80-70-60. The child did not vomit. The somnolence was continuous, and bathing, changing, etc., did not awake her. During the six days of her life she did not emit a cry. The movements of the body and extremities were very feeble, the arms were somewhat contracted; no loss of tendon reflexes, or of sensibility to pain. At the age of six days she died.

At necropsy 280 c.c. of clear fluid escaped. There were no cerebral hemispheres, corpus callosum nor fornix cerebri. There was only a thin, 1-mm.-thick sac of cerebral substance. In behind the sella turcica there was a cystic pineal gland about the size of an almond; it rested on the corpora quadrigemina, and obliterated the aqueduct of Sylvius. The anterior corpora quadrigemina were ttened. The cerebellum, pons, corpora quadrigemina, spinal cord, and fourth entricle were all normal.

48. Meyer's Case.[50]—Meyer presented this case before the New York Neurological Society first in 1902, as a lesion of the chiasm, and escape of cerebrospinal fluid from the nose, and later (January, 1905), pathological specimens were presented. The patient, a male, struck his head while diving in 1894. In 1898 he became blind. In 1899, he had transitory attacks of numbness on the left side of the face, leaving out part of the area of the middle branch. Then followed difficulty in moving the jaw to the left. In 1900 cerebrospinal fluid began to drip from the right nostril, with some general relief. On stopping the patient would become sleepy and stuporous. At one time he showed a strong tendency to walk in a circle. In May and October, 1902, being then 22 years old, he had several

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49. Joukovsky, V.: Hydrocèphalie et tumeur congenitale de la glande pinéale chez un nouveau né, Rev. mens. d. mal. de l'enf., 1901, xix, 197.

50. Meyer, A.: Adenoma of Pineal Gland, Jour. of Nerv. and Ment. Dis., 1903, xxx, 216; 1905, xxxii, 464.

general convulsions, and he died in 1904 in status epilepticus. There were no other neurological signs reported, save slight increase in the knee-jerks.

Necropsy showed an adenoma of the pineal gland. It had pressed itself through the roof of the mid brain, behind the posterior commissure, protruding into the third and fourth ventricle, and displacing the corpora quadrigemina.

49. ASKANAZY'S CASE.[51]—Male, aged 19, in January, 1906, began to have headaches and then pains in the neck which were so severe that he could not hold his head quiet. On going to work January 10, he had an attack of giddiness and fell to the ground without any loss of consciousness. Three days later he vomited and lost consciousness for ten minutes, and was sent to the hospital where he vomited again repeatedly. He was slightly dull; the knee-jerks were increased, especially on the right side; no clonus; no Babinski; Kernig and Lasègue both positive. Lumbar puncture was negative. The patient's condition remained stationary until January 17, when he suddenly became worse. Headaches were severe, vomiting was excessive and he had an epileptiform attack lasting one minute. The right pupil was dilated, the left contracted; pulse 50 to 60. The patient died January 18.

Necropsy showed subarachnoid edema; the ventricles were not dilated. The slightly dilated third ventricle contained blood; also a coherent bloody mass which reached in the direction of the quadrigemina. It lay between the posterior commissure, and the cerebellar vermis, and was about as big as a walnut. It could be removed *in toto*. It covered the entire quadrigeminal region, reaching further left than right. It caused an area of softening in the left corpora geniculata and in the pulvinar of the left thalamus, as well as softening the corpora quadrigemina and opening the aqueduct of Sylvius. There was a bloody infiltration into the cerebellum. The tumor was a chorio-epithelioma, and the author discusses the interesting relation between chorio-epitheliomata and teratomata.

50. VERGER'S CASE.[52]—Inadequately reported case of a woman, aged 42, who was first observed in a marked state of dementia. She hardly answered questions, but ate, drank and slept; no palsies, nor ocular symptoms recorded; she had headache. Towards the close of her illness she had marked vertigo, generalized rigors and opisthonos; tendon reflexes exaggerated both sides.

Necropsy showed hydrocephalus, and a gliosarcomatous tumor the size of a hen's egg. It filled and distended the third ventricle, pressing up against the corpus callosum.

51. CHIRONE'S CASE.[53]—Chirone speaks of a figure done in wax of a hydrops of the pineal 4 by 5 cm. by P. E. Sorrentino in 1845, and preserved in the anatomical museum of the Hospital of S. M. d. Loreta of Naples. He also gives a short summary of some twenty or more cases from literature.

52. MARBURG'S CASE.[54]—B. L., girl, aged 9, always delicate and weakly, in October, 1906, began to see badly and could not write as formerly. Six weeks later she began to have rheumatic-like pains in the neck, head, arms and legs, which were relieved somewhat by medication. Examination of the fundi showed signs of pressure. In March following, headache was severe, and the patient was compelled to go to bed; vomiting took place. Two weeks later, on trying to walk she staggered, and she had such ataxia of the arms as to be unable to feed herself. The circumference of the head had increased 6 cm. from October, 1906, to October, 1907. The intelligence was not much affected. The patient began to get fatter.

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51. Askanazy, M.: Teratom und Chorioepitheliom der Zirbel, Verhandl. d. deutsch. path. Gesellsch., 1906, p. 58.

52. Verger, M.: Gliosarcoma developpé au niveau de la glande pinéale, Jour. de méd. de Bordeaux, 1907, xxxvii, 216.

53. Chirone, P.: I tumori della glandula pineale, Med. ital., 1907, v, 141.

54. Marburg, O.: Zur Kenntnis der normalen und pathologischen Histologie der Zirbeldrüse, Die Adipositas cerebralis, Arb. a. d. Neur. Inst., 1909, xvii, 217; also Wien. med. Wchnschr., 1907, lii, 1908, No. 48.

In October, 1907, the patient's measurements were 123 cm. in height, 66 cm. breast measure, 70 abdomen. The skin was smooth and dry and there was marked panniculus; weight 29.3 kg. The patient had choked disks, and slight flattening of right nasolabial fold. Otherwise the cranial nerve-findings were negative. The upper extremities showed less motor power of left side, but the right reflexes were more active. No tremor of hands, but a marked ataxia in the finger-finger, and finger-nose tests; left more than right; adiadokokinesis of both hands; abdominal reflexes both sides somewhat diminished; lower extremities showed diminished motor power; slight spasms; knee-jerks increased; ankle-clonus present on right side; Babinski sign present; ataxia of both lower limbs on knee-heel test; cerebellar asynergia. Walking alone was impossible; spastic ataxia; slight fainting attacks. October, 1907, body weight increased and heart-beat was rapid—120 to 140. Palliative trephining was done by Eiselsberg, over the cerebellum, as a cerebellar lesion was diagnosed; tumor sought for and not found. Patient died.

Necropsy showed a mixed tumor of the pineal, compressing the left pulvinar, and reaching to the anterior corpora quadrigemina. There was some hydrocephalus; hypophysis normal, as well as all other blood glands.

53. HART'S CASE.[55]—Male, aged 24, for three weeks preceding admission had severe headaches, nausea and increasing fatigability. There was stiffness of the neck, optic neuritis, with reduced vision, slowed pulse and leukocytes in the spinal fluid. As the patient had a fetid bronchial discharge a brain abscess was suspected. The patient died in seven weeks.

Necropsy showed internal hydrocephalus, soft hemorrhagic angiosarcoma of the pineal, third ventricle much dilated, partially filled with tumor fragments. Posteriorly the tumor rested on the corpora quadrigemina, infiltrating and substituting the structures in part.

54. FRANKL-HOCHWART'S CASE.[56]—Boy 5½ years old. At the age of 3 the child began to grow very rapidly and at 5 he was stout and had reached the size of a boy of 7. The boy also developed rapidly mentally, occupied himself with the question of immortality, and of the life after death. In August, 1908, he developed strabismus. In December he had headache, was very sleepy, yawned a great deal; no vomiting. In December he had scarlatina with fever, vomiting and angina, from which he recovered, but remained sleepy and apathetic, and the headache increased. From the early part of December, 1908, there was a striking development of the penis, and marked genital hair, also small hair on the skin. The patient had frequent erections and the voice was very deep.

In January, 1909, patient was as big as a boy of 9; 123 cm. long; moderate fatty deposits; bones proportionately developed; penis 7 cm. long; hair on genitals like a 15-year-old boy; pupillary reactions sluggish; abducens paralyzed both sides; rectus inferior and superior on both sides paralyzed; left internus paretic, right normal; field of vision contracted; right eye much contracted on temporal side; double choked disk; cranial nerves otherwise normal; slight tremor of left arm. The patient grew more sleepy, and the headache was worse. Urinary incontinence, vomiting and epileptiform convulsions appeared in January, and January 22 he died in coma.

Necropsy showed a definite hydrocephalus, and a walnut-sized tumor in the pineal region (5 by 2.5 by 2.9 cm.) soft and knobby, fastened to the vena magna. The third ventricle was dilated, especially above; the superior vermis was slightly flattened. The roof of the aqueduct was lacking in its anterior half. The tumor had replaced the pineal and compressed the aqueduct; the corpora quadrigemina were compressed and pushed to one side. The tumor was a teratoma.

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55. Hart, C.: Ein Fall von Angiosarkom der Glandula pinealis, Berl. klin. Wchnschr., 1909, xlvi, 2298.

56. Frankl-Hochwart: Ueber Diagnose der Zirbeldrüsentumoren, Deutsch. Ztschr. f. Nervenh., 1909, xxxvii, 455.

55. PAPPENHEIM'S CASE.[57]—L. R., aged 10, a well-nourished boy, entered the Freiburg eye clinic complaining of having had a headache for four weeks, with vomiting, for which he was compelled to go to bed. This continued up to the time of his entering the clinic, when he began to notice diminution in his vision. His head was large; pupils showed light and accommodation reflexes (?); reflexes were increased throughout; traces of a patellar clonus; no mental anomalies; choked disks were present. Shortly after a decompression operation the patient showed increasing dulness and died.

Necropsy showed external and internal hydrocephalus, and a walnut-sized tumor of the pineal gland. It occupied the posterior part of the third ventricle, lying on and involving the substance of the corpora quadrigemina. Muscle-like cells were found, but no other tissues resembling a teratoma. Pappenheim groups it as one of Marburg's compound tumors of the pineal, and terms it a neuroglioma ependymale. He collects reports of thirty-seven cases.

56. RAYMOND AND CLAUDE'S CASE.[58]—M. B., a boy aged 10, well up to the age of 7, was large for his age, and well developed mentally. In January, 1906, he commenced to have a headache localized on the right side, radiating toward the eye, the nose and the superior maxillary region of the same side. He vomited, with severe crises of pain. He grew somewhat better until July, 1907, when the headache and vomiting reappeared. He then began to grow fat, and was large for his age. He grew weak rapidly. In October the left leg was feeble; the patient could hardly raise it from the ground. His eyesight became impaired, and his eyes had a tendency to turn to the left. Lumbar puncture gave some relief. In January, 1908, blindness was complete. Vomiting was made worse by a lumbar puncture.

His parents brought him to France in May, 1909. At that time he was 138 cm. tall, looking like a boy of 13. The skin was fat. The patient weighed 39 kilos; boys of his age should weigh 25 to 26 kilos. He was apathetic, did not speak spontaneously, but answered questions well. The cranium was enlarged. The patient was muscularly weak, especially on the left side. There was light paresis of the muscles of the face on the left side. The tendon reflexes showed slight spasticity. There was a normal knee-jerk, but there was clonus and Babinski on both sides; upper extremities normal. The abdominal reflexes seemed diminished. There was bilateral optic atrophy; the pupils were dilated and immobile, and there was slight nystagmus. The genital organs were small and the testicles very small. The patient grew more and more apathetic and sleepy. In July the cranial sutures seemed to be coming apart; percussion gave a cracked-pot sound. Contractures of the neck and arms then developed. In October, 1909, the child died of bronchopneumonia.

Necropsy showed marked hydrocephalus; the third ventricle was dilated, and there was a tumor of the pineal 4 cm. in diameter. The corpora quadrigemina were not recognizable from pressure. The pons was also involved by the tumor. It was a glioma.

57. HOWELL'S CASE[59] 1.—P. L., male, aged 42, had complained of dimness of vision and occipital headaches for six months, the latter having remitted somewhat for two months. He was also giddy at times and had a tendency to fall to the left, and also to fall backward. He staggered to the left in walking. Five months after the onset he had had diplopia. On admission he had recent optic neuritis, loss of upward movement of the eyeballs, impairment of downward motion, especially in the right; pupils small and inactive to light and con-

57. Pappenheim, A. W.: Ueber Geschwülste des Corpora pineale, Virchows Arch. f. path. Anat., 1910, cc, 122.

58. Raymond and Claude: Les tumeurs de la glande pinéale, Bull. de l'Acad. de méd., March 15, 1910.

59. Howell: Tumors of the Pineal Body, Proc. Roy. Soc. Med., 1910, iii, No. 5, 77.

vergence; left abdominal reflex diminished; cerebellar operation, with death six weeks later.

Necropsy showed considerable flattening of the convolutions; some ventricular distention; pons was widened and flattened, as also the peduncles, and ventral portion of the mid-brain. A (gliosarcomatous?) tumor extending from the posterior commissure, to the valve of Vieussens was found. The tumor occupied the aqueduct and dorsal part of mid-brain. It distended rather than infiltrated the tissues, save in the medial parts of the thalami, where there was some infiltration. The cerebrospinal, central tegumental and right tectospinal tracts showed recent degenerations.

58. Howell's Case 2.—B., male, aged 22, had nausea and slight sickness (vomiting?) for some months. For three months he had to stop work owing to vertigo, and he had some slight ptosis. For six weeks he had been getting stupid and inattentive; had tremor in hands and uncertainty of gait; headache and diplopia for two weeks; was healthy-looking, but very restless. He was somewhat deaf, was very thirsty, and drank enormously of water.

Examination showed optic neuritis, pupils equal, ectopic upward and inward, inactive to light and accommodation, loss of upper eye movements, with later oscillation on motion; downward motion incomplete; slight paresis of left external rectus; slight ptosis, slight deafness; rhythmical tremor of both upper extremities; ataxia both sides; gait uncertain; anomalous shuddering movement of upper limbs, without sensation of being cold.

Necropsy showed increased hydrocephalus, the floor of the third ventricle being bulged out as a thin walled cyst. A walnut-sized, friable tumor (gliosarcoma?) was found projecting into the dilated third ventricle from behind. The aqueduct was dilated, and so filled with the growth that its roof was disrupted, the growth had also gone down into the fourth ventricle. There were no distinct infiltrations.

59. Howell's Case 3.—F. L., male, 20 years old, had constant headaches, and weakness for five months. His legs gave way when he walked. He had failing memory and giddiness; no rotation. Examination showed smell defective, intense optic neuritis, pupils sluggish to light and convergence; oval on dilatation; loss of upward motion of the eyes, nystagmus on lateral movements; slight left facial weakness; considerable weakness in left leg and arm, and in back muscles; tendency to fall backward; some incoordination of right arm. Death after operation to relieve pressure.

Necropsy showed marked hydrocephalus, with distention of floor of third ventricle; pons and mid-brain much flattened. Tumor (gliosarcoma?) of pineal body blocking aqueduct, also forcing into it, distending it and causing it to rupture through the upper part of the roof; slight infiltration of thalami; degenerations in posterior longitudinal bundle, and ventral longitudinal bundle, tegmental tracts and both cerebellar peduncles; mesial fillet fiber degenerations.

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INDEX TO VOLUME VIII

PAGE

Adrenal, malignant tumors of; B. F. Davis 60
Albumin and albumose in the sputum and their relation to occult blood, diagnostic importance of; E. H. Goodman 163
Alimentary canal, importance of tonus for the movements of; W. B. Cannon. 417
Ameboid movements in macrocytes and megaloblasts; R. S. Morris, and W. S. Thayer 581
Anesthesia, glycosuria after; P. B. Hawk 39
"Aorta and Heart, Diseases of," by Arthur D. Hirschfelder, review of 262
Arterial lesions and acute infectious diseases; C. Frothingham, Jr. 153
Atrophy, subacute, of liver; L. S. Milne 639
Auer, J.: Intravenous injection of salvarsan in acid solution 169

Bacillus-carrier, typhoid, recovery of during vaccine treatment; W. V. Brem and F. C. Watson 630
Bacillus influenzæ, cerebrospinal meningitis due to; L. J. Rhea 133
Bailey, Pearce and Jelliffe, Smith Ely: Tumors of the pineal body 851
Barbour, Henry G.: Nitrogen and fat metabolism and other functional tests in a case of chronic pancreatitis 662
Bile-ducts, congenital obliteration of; C. P. Howard and S. B. Wolbach 557
Blood, coagulation-time of the, as affected by various conditions; M. S. Cohen 684, 820
Blood-flow in the arm, effect of some hydrotherapeutic procedures on; A. W. Hewlett, J. G. Van Zwaluwenburg and Mark Marshall 591
Blood, occult, relation of, to albumin and albumose in the sputum; E. H. Goodman 163
Boggs, Thomas R.: Percussion signs of persistent or enlarged thymus 659
Boggs, Thomas R., and Morris, Roger S.: Leukocytic enzymes in leukemia in neutral media 806
Bookman, A.: Metabolism in a case of idiopathic osteopsathyrosis 675
Book Reviews—
Fenwick's "Dyspepsia: Its Varieties and Treatment" 130
Hirschfelder's "Diseases of the Heart and Aorta" 262
Morrow's "Diagnostic and Therapeutic Technic" 131
Sahli's "Treatise on Diagnostic Methods of Examination" 263
Brem, Walter V., and Watson, F. C.: Recovery of a typhoid bacillus-carrier during vaccine treatment 630
Brill's symptom-complex, typhus fever and Manchurian typhus; G. A. Friedman 427

Cancer, incoagulable nitrogen of puncture fluids with special reference to; R. S. Morris 457
Cancer, observations on the hemolytic skin test for; L. M. Warfield 621
Cannon, Walter B.: Importance of tonus for the movements of the alimentary canal 417
Capps, Joseph A.: An experimental study of the pain sense in the pleural membranes 717

PAGE

Carcinoma, primary, of the liver, clinicopathological study of; H. T. Karsner 238
Cardiorenal disease, experimental; H. A. Christian, R. M. Smith and I. C. Walker 468
Caulfeild, Alfred H.: Correlation of clinical progress with the results of immunological studies in pulmonary tuberculosis..... 440
Cecil, Russell L. and Soper, Willard B.: Meningococcus endocarditis, with septicemia 1
Cerebrospinal meningitis due to *Bacillus influenzæ;* L. J. Rhea..... 133
Christian, Henry A., Smith, R. M., and Walker, I. Chandler: Experimental cardiorenal disease 468
Cohen, Myer Solis: Coagulation-time of the blood as affected by various conditions 684, 820
Craig, Charles F.: Immediate effect on the complement fixation test for lues of treatment with salvarsan 395

Davis, Benjamin F.: Malignant tumors of the adrenal..... 60
De Sautelle, W. T. and Grey, E. G.: The relation of the papillary muscles to mitral regurgitant murmurs..... 734
"Diagnostic and Therapeutic Technic," by Albert S. Morrow, review of.... 131
"Diagnostic Methods of Examination," by Hermann Sahli, review of..... 263
Duodenal diagnosis: *x*-ray considerations; E. H. Skinner..... 574
"Dyspepsia: Its Varieties and Treatment," by W. Soltau Fenwick, review of. 130

Edema of the pia-arachnoid; C. K. Stillman..... 193
Emerson, Haven: Fracture of cervical vertebræ, resulting in hypotonia and hypothermia 150
Endocarditis, meningococcus, with septicemia; R. L. Cecil and W. B. Soper.. 1
Enzymes, leukocytic, in neutral media, in leukemia; Roger S. Morris and Thomas R. Boggs..... 806
Epiphysis, tumors of; P. Bailey and S. E. Jelliffe 851
Ether anesthesia, urine formation during; P. B. Hawk..... 177
"Examination, Diagnostic Methods of," by Hermann Sahli, review of..... 263
Exudates, serous, diagnostic value of mitotic figures in the cells of; L. F. Warren 648

Fat and nitrogen metabolism, and other functional tests in a case of chronic pancreatitis; H. G. Barbour..... 662
Fenwick's "Dyspepsia: Its Varieties and Treatment," review of..... 130
Fluoroscopy in duodenal diagnosis; E. H. Skinner..... 574
Fracture of cervical vertebræ resulting in hypotonia and hypothermia; H. Emerson 150
Friedman, G. A.: Brill's symptom-complex; typhus fever; Manchurian typhus 427
Frothingham, Channing, Jr.: Acute infectious diseases and arterial lesions .. 153

Glycosuria, postanesthetic; P. B. Hawk..... 39
Glycosuria, postanesthetic, of surgical patients; J. M. Swan..... 58
Goiter, exophthalmic, pathological anatomy of; D. Marine and C. H. Lenhart 265
Goodman, Edward H.: Diagnostic importance of albumin and albumose in the sputum and their relation to occult blood..... 163
Grey, E. G. and De Sautelle, W. T.: Relation of the papillary muscles to mitral regurgitant murmurs..... 734

PAGE

Hawk, P. B.: Modification of Wohlgemuth's method for the quantitative study of the activity of the pancreatic function 552
Hawk, P. B.: Postanesthetic glycosuria 39
Hawk, P. B.: Studies on water-drinking 382
Hawk, P. B.: Urine formation during ether anesthesia 177
"Heart and Aorta, Diseases of," by Arthur D. Hirschfelder, review of 262
Heart and kidney; see Cardiorenal
Heart, influence of temperature on the output of; H. F. Wolf 463
Heart murmurs (mitral regurgitant), relation of papillary muscles to; W. T. De Sautelle and E. G. Grey 734
Heart-block, observations on; J. G. Van Zwaluwenburg 141
Hemochromatosis; T. P. Sprunt 75
Hemolytic skin test for cancer, observations on; Louis M. Warfield 621
Hemoptysis, physiological investigation of the treatment in; C. J. Wiggers .. 17
Hewlett, A. W., Van Zwaluwenburg, J. G., and Marshall, Mark: Effect of some hydrotherapeutic procedures on the blood-flow in the arm 591
Hill, E. W.: Tetanus 747
Hirschfelder's "Diseases of the Heart and Aorta," review of 262
Howard, C. P., and Wolbach, S. B.: Congenital obliteration of the bile-ducts 557
Hydrotherapeutic procedures, effect of, on the blood-flow in the arm; A. W. Hewlett, J. G. Van Zwaluwenburg and Mark Marshall 591
Hypothermia and hypotonia, fracture of cervical vertebræ resulting in; H. Emerson 150

Immunological studies in pulmonary tuberculosis, correlation of clinical progress with; A. H. Caulfeild 440
Infectious diseases, acute and arterial lesions; C. Frothingham, Jr. 153
Influenza bacillus, cerebrospinal meningitis due to; L. J. Rhea 133

Jelliffe, Smith Ely and Bailey, Pearce; Tumors of the pineal body 851

Karsner, Howard T.: Clinicopathological study of primary carcinoma of the liver 238
Kennedy, Foster: Symptomatology of temporosphenoidal tumors 317
Kidney and heart; see Cardiorenal

Lenhart, C. H., and Marine, David: Pathological anatomy of exophthalmic goiter 265
Leukemia, leukocytic enzymes, in neutral media, in; R. S. Morris and T. R. Boggs 806
Liver atrophy, subacute; L. S. Milne 639
Liver, clinicopathological study of primary carcinoma of; H. T. Karsner .. 238
Lues, immediate effect on the complement fixation test for, of treatment with salvarsan (arsenobenzol); C. F. Craig 395

Macrocytes and megaloblasts, ameboid movements in; R. S. Morris, and W. S. Thayer 581
Manchurian typhus, Brill's symptom-complex and typhus fever; G. A. Friedman 427
Marine, David and Lenhart, C. H.: Pathological anatomy of exophthalmic goiter 265
Marshall, Mark, Hewlett, A. W., and Van Zwaluwenburg, J. G.; Effect of some hydrotherapeutic procedures on the blood-flow in the arm 591

PAGE

May, James V.: Laboratory diagnosis of general paresis 183
McCord, Carey P.: Investigation of the depressor action of pituitary extracts 609
Megaloblasts and macrocytes, ameboid movements in; R. S. Morris and W. S. Thayer 581
Meningitis, cerebrospinal, due to *Bacillus influenzæ;* L. J. Rhea 133
Meningococcus endocarditis, with septicemia; R. L. Cecil and W. B. Soper .. 1
Metabolism in a case of idiopathic osteopsathyrosis; A. Bookman 675
Metabolism, nitrogen and fat, and other functional tests in a case of chronic pancreatitis; H. G. Barbour 662
Milne, Lindsay S.: Subacute liver atrophy 639
Mitotic figures in the cells of serous exudates, diagnostic value of; L. F. Warren 648
Mitral regurgitant murmurs, relation of the papillary muscles to; W. T. De Sautelle and E. G. Grey 734
Morris, Roger S.: Incoagulable nitrogen of puncture fluids, with special reference to cancer 457
Morris, Roger S. and Boggs, Thomas R.: Leukocytic enzymes in leukemia in neutral media 806
Morris, Roger S., and Thayer, William S.: Ameboid movements in macrocytes and megaloblasts 581
Morrow's "Diagnostic and Therapeutic Technic," review of 131
Muscles, papillary, and mitral regurgitant murmurs; W. T. De Sautelle and E. G. Grey 734

Nitrogen and fat metabolism and other functional tests in a case of chronic pancreatitis; H. G. Barbour 662

Osteopsathyrosis, idiopathic, metabolism in a case of; A. Bookman 675

Pain sense in the pleural membranes, experimental study of; J. A. Capps ... 717
Pancreatic function, modification of Wohlgemuth's method for the quantitative study of the activity of; P. B. Hawk 552
Pancreatitis, chronic, nitrogen and fat metabolism in; H. G. Barbour 662
Paresis, general, laboratory diagnosis of; James V. May 183
Percussion signs of persistent or enlarged thymus; T. R. Boggs 659
Pia-arachnoid, edema of; C. K. Stillman 193
Pineal body, tumors of; P. Bailey and S. E. Jelliffe 851
Pituitary extracts, an investigation of the depressor action of; Carey P. McCord 609
Pleural membranes, an experimental study of the pain sense in; Joseph A. Capps 717
Postanesthetic glycosuria; P. B. Hawk 39
Postanesthetic glycosuria of surgical patients; J. M. Swan 58
Proescher, Frederic: Preventive treatment of rabies with unchanged virus fixe 351
Proteins, consideration of some chemical transformations of, and their possible bearing on problems in pathology; F. P. Underhill 356
Puncture fluids, incoagulable nitrogen of, with special reference to cancer; Roger S. Morris 457

Rabies, further experience in preventive treatment of, with unchganged virus fixe; F. Proescher 351
Rhea, Lawrence J.: Cerebrospinal meningitis due to *Bacillus influenzæ* 133
Roentgen ray in duodenal diagnosis; E. H. Skinner 574

PAGE

Sahli's "Treatise on Diagnostic Methods of Examination," review of..... 263
Salicylates of natural and synthetic origin, a comparative investigation of the effects and toxicity of; J. A. Waddell..... 784
Salvarsan, immediate effect on the complement fixation test for lues of treatment with; C. F. Craig 395
Salvarsan in acid solution, experiments with the intravenous injection of; J. Auer 169
Septicemia and meningococcus endocarditis; R. L. Cecil and W. B. Soper.... 1
Skinner, E. H.: Duodenal diagnosis: *x*-ray considerations..... 574
Skin test, hemolytic, for cancer, observations on; Louis M. Warfield..... 621
Smith, R. M., Christian, H. A., and Walker, Chandler I.: Experimental cardiorenal disease 468
Sodium salicylates of natural and synthetic origin, a comparative investigation of the effects and toxicity of; J. A. Waddell..... 784
Soper, Willard B. and Cecil, Russell L.: Meningococcus endocarditis, with septicemia 1
Sprunt, T. P.: Hemochromatosis 75
Sputum, albumin and albumose in, diagnostic importance of, and relation to occult blood; E. H. Goodman..... 163
Stillman, Charles K.: Edema of the pia-arachnoid..... 193
Surgical patients, postanesthetic glycosuria of; J. M. Swan..... 58
Syphilis, immediate effect on the complement fixation test for, of treatment with salvarsan; C. F. Craig 395
Swan, John M.: Postanesthetic glycosuria of surgical patients..... 58

Temperature, influence of, on the output of the heart; H. F. Wolf..... 463
Temporosphenoidal tumors, symptomatology of; F. Kennedy..... 317
Test, complement fixation, for syphilis, immediate effect on, of treatment with salvarsan; C. F. Craig 395
Test, hemolytic skin, for cancer, observations on; L. M. Warfield..... 621
Tetanus; E. W. Hill 747
Thayer, William S., and Morris, Roger S.: Ameboid movements in macrocytes and megaloblasts 581
"Therapeutic and Diagnostic Technic," by Albert S. Morrow, review of.... 131
Thymus, persistent or enlarged percussion signs of; Thomas R. Boggs..... 659
Tonus, importance of, for the movements of the alimentary canal; W. B. Cannon 417
Tuberculosis, pulmonary, correlation of clinical progress with the results of immunological studies in; A. H. Caulfeild..... 440
Tumors, malignant, of the adrenal; B. F. Davis..... 60
Tumors of the pineal body; P. Bailey and S. E. Jelliffe..... 851
Tumors, temporosphenoidal, symptomatology of; Foster Kennedy..... 317
Typhoid bacillus-carrier, recovery of, during vaccine treatment; Walter V. Brem and F. C. Watson..... 630
Typhus fever, Manchurian typhus, and Brill's symptom-complex; G. A. Friedman 427

Underhill, Frank P.: Some chemical transformations of proteins and their possible bearing on problems in pathology..... 356
Urine formation during ether anesthesia; P. B. Hawk..... 177

Vaccine treatment, recovery of a typhoid bacillus-carrier during; W. V. Brem and F. C. Watson 630

PAGE

Van Zwaluwenburg, J. G., Hewlett, A. W., and Marshall, Mark: Effect of some hydrotherapeutic procedures on the blood-flow in the arm..... 591

Vertebræ, cervical, fracture of, resulting in hypotonia and hypothermia; H. Emerson 150

Virus fixe, unchanged, further experience in the preventive treatment of rabies with; F. Proescher 351

Waddell, J. A.: A comparative investigation of the effects and toxicity of sodium salicylates of natural and synthetic origin..... 784

Walker, I. Chandler, Christian, H. A., and Smith, R. M.: Experimental cardiorenal disease 468

Warfield, Louis M.: Hemolytic skin test for cancer..... 621

Warren, L. F.: Diagnostic value of mitotic figures in the cells of serous exudates 648

Water-drinking, studies on; P. B. Hawk..... 382

Watson, F. C., and Brem, Walter V.: Recovery of a typhoid bacillus-carrier during vaccine treatment 630

Wiggers, Carl J.: Physiological investigation of the treatment in hemoptysis 17

Wohlgemuth's method for the quantitative study of the activity of the pancreatic function, modification of; P. B. Hawk..... 552

Wolbach, S. B., and Howard, C. P.: Congenital obliteration of the bile-ducts 557

Wolf, Heinrich F.: Influence of temperature on the output of the heart.... 463

X-ray considerations in duodenal diagnosis; E. H. Skinner..... 574

Zwaluwenburg, Van, James G.: Observations on heart-block..... 141

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VOLUME 8 NUMBER 6

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CONTENTS OF VOLUME VIII

SEPTEMBER, 1911. NUMBER 3.

PAGE

Pathological Anatomy of Exophthalmic Goiter. The Anatomical and Pathological Relations of the Thyroid Gland to this Disease; the Treatment. David Marine, M.D., and C. H. Lenhart, M.D., Cleveland, Ohio 285

The Symptomatology of Thrombo-Endocardial Tuberculosis. Pearce Kintzing, M.D., B.Ch. (Oxon.'s), New York 317

Further Experience in the Preventive Treatment of Rabies with Unchanged Virus Fixe. Joseph Frothingham, M.D., Pittsburgh 361

A Consideration of Some Chemical Transformations of Proteins and Their Possible Bearing on Problems in Pathology. Frank P. Underhill, New Haven, Conn. 366

Studies on Water-Drinking. VI. The Activity of the Pancreatic Juice Under the Influence of Copious and Moderate Water-Drinking with Meals. P. B. Hawk, Ph.D., Urbana, Ill. 382

The Immediate Effect of the Complement Fixation Test and Line of Treatment with Salvarsan (Arsenobenzol). An Analysis of 225 Cases. Charles P. Craig, M.D., Washington, D.C. 387

OCTOBER 1911. NUMBER 4.

PAGE

The Importance of Tetanus for the Maintenance of the Alimentary Canal. Walter B. Cannon, M.D., Boston 417

Bence's Stenton-Counter; Typhus Fever; Manchurian Typhus. A. Periman, M.D., New York 427

Correlation of Clinical Progress With the Results of Bacteriological Studies in Pulmonary Tuberculosis. Alfred H. Carswell, M.B., Gravenhurst, Ont. 435

The Intracellular Nitrogen of Pyocyaneus Fevers, With Special Reference to Cancer. A Preliminary Note. Roger S. Morris, M.D., St. Louis 457

The Influence of Temperature on the Output of the Heart. Heinrich P. Wolf, M.D., New York 469

Experimental Cardiovascular Disease. Henry A. Christian, M.D., R. M. Smith, M.D., and L. Chandler Walker, M.D., Boston 486

A Modification of Worlidge's Method for the Quantitative Study of the Activity of the Pancreatic Function. P. B. Hawk, Ph.D., Urbana, Ill. 497

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CONTENTS

PAGE

I. Cholecystenterostomy: Obliteration of the Gall-Duct by Ligature. By [illegible], M.D., Iowa City, Iowa, and S. R. Wolfard, M.D., Keokuk 607

II. Acute Pancreatitis: Some Considerations. By [illegible] Francoscopy. By H. Schlesinger, M.D., Los Angeles, Cal., and [illegible], Mo. 615

III. Abnormal Movements in Diagnostics and Mechanotherapy. By [illegible], M.D., St. Louis, and William S. [illegible], M.D., Baltimore 623

IV. The Physiology of Some Hydrotherapeutic Procedures on the Blood-Flow in the Arm. By R. W. Hiscox, M.D., [illegible] Van Swaluwenburg, M.D., Mark [illegible], and [illegible], South Ardsley, Mich. 627

V. Experimental Investigations of the Depressor Action of Strophanthus. By Henry P. McCord, [illegible], Ann Arbor, Mich. 639

VI. Observations on the Blood and Skin Test for Diabetes. By [illegible] Warfield, M.D., Milwaukee, Wis. 651

VII. Report of a Typhoid Fever Carrier Discovered in Connection with Operative Treatment. By [illegible] Bebb, M.D., Los Angeles, Cal., and [illegible], M.D., Corozal, Canal Zone 655

VIII. Primary Liver Abscess. By Henry N. Milne, [illegible] 659

IX. [illegible] Value of Negative Findings in the Serious Extremities. By P. Wa[illegible], M.D., Ann Arbor, Mich. 665

X. Peculiar Stones of Pleasantry or Enjoyment. By Reginald R. Bloor, M.D., Baltimore 669

XI. Hypertrophy and Fat Metabolism and Other Personal Notes: A Case of Chronic Pancreatitis. By Henry [illegible], M.D., Baltimore 669

XII. [illegible] Problem in a Case of Idiopathic [illegible] By [illegible], Bookman, M.D., New York 673

XIII. [illegible] Considerations-Time of the Blood as [illegible] Conditions (Other Continued). By [illegible], M.D., Philadelphia 675

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